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PROCEEDINGS

OF THE

PATHOLOGICAL SOCIETY

OF PHILADELPHIA.

NEW SERIES, VOLUME IX.
OLD SERIES, VOLUME XXVII.

CONTAINING THE TRANSACTIONS OF THE SOCIETY FROM SEPTEMBER, 1905, TO JANUARY, 1907.

EDITED BY

D. L. EDSALL, M.D.,

RECORDER OF THE SOCIETY.

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PHILADELPHIA:
PRINTED FOR THE SOCIETY BY WM. J. DORNAN.
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FORMER PRESIDENTS.

SAMUEL D. GROSS, M.D., LL.D., D.C.L. Oxon., LL.D. Cantab., elected 1857.

RENÉ LA ROCHE, M.D., elected 1858.

ALFRED STILLÉ, M.D., LL.D., elected 1859, 1861, and 1862.

EDWARD HARTSHORNE, M.D., elected 1860 and 1863.

J. M. DA COSTA, M.D., LL.D., elected 1864, 1865, and 1866.

JOHN H. PACKARD, M.D., elected 1867 and 1868.

S. WEIR MITCHELL, M.D., LL.D., elected 1869.

JOHN ASHHURST, Jr., M.D., LL.D., elected 1870.

JAMES H. HUTCHINSON, M.D., elected 1871 and 1872.

WILLIAM PEPPER, M.D., LL.D., elected 1873.

H. LENOX HODGE, M.D., elected 1876.

S. W. GROSS, M.D., elected 1879.

JAMES TYSON, M.D., elected 1882 and 1883.

E. O. SHAKESPEARE, M.D., elected 1884.

J. C. WILSON, M.D., elected 1885 and 1886.

F. P. HENRY, M.D., elected 1887 and 1888.

HENRY F. FORMAD, M.D., elected 1889 and 1890.

ARTHUR V. MEIGS, M.D., elected 1891 and 1892.

J. H. MUSSER, M.D., elected 1893, 1894, 1895, and 1896.

W. E. HUGHES, M.D., elected 1897 and 1898.

F. A. PACKARD, M.D., elected 1899 and 1900.

CHARLES W. BURR, M.D., elected 1901 and 1902.

ALFRED STENGEL, M.D., elected 1903 and 1904.

W. M. L. COPLIN, M.D., elected 1905.

OFFICERS AND COMMITTEES

OF THE

PATHOLOGICAL SOCIETY OF PHILADELPHIA.

(List of officers elected October 12, 1905.)

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LIST OF MEMBERS.

ORIGINAL MEMBERS.

JAMES DARRACH, 5923 Greene Street, Germantown.
S. WEIR MITCHELL, 1524 Walnut Street.
GEORGE C. HARLAN, 1700 Walnut Street.

MEMBERS.

ELECTED
1894 Abbott, A. C., 4229 Baltimore Avenue.
1907 Addison, W. H. H., 3928 Pine Street.
1899 Adler, L. H., Jr., 1610 Arch Street.
1907 Allen, Alfred Reginald, 111 South Twenty-first Street.
1903 Allen, F. O., 323 South Sixteenth Street.
1898 Allen, L. M., 3100 Wharton Street.
1906 Allyn, Herman B., 501 South Forty-second Street.
1889 Anders, J. M., 1605 Walnut Street.
1901 Anspach, B. M., 4813 Baltimore Avenue.
1906 d'Apery, Tello J., 767 North Fortieth Street.
1900 Artelt, H., 1521 North Eighth Street.
1891 Ashton, Thomas G., 1814 South Rittenhouse Square.
1895 Ashton, William E., 2011 Walnut Street.

1897 Babcock, W. Wayne, 3302 North Broad Street.
1887 Baker, G. F., 1818 Spruce Street.
1888 Balliet, Tilghman M., 3709 Powelton Avenue.
1906 Beardsley, E. J. G., 2030 Chestnut Street.
1885 Beates, Henry, Jr., 260 South Sixteenth Street.
1900 Behrend, Moses, 1331 North Franklin Street.
1871 Bennett, Wm. H., 1837 Chestnut Street.
1887 Berens, Bernard, 2041 Chestnut Street.
1900 Bergey, D. H., 3965 Brown Street.
1905 Bernheim, Albert, 1411 Spruce Street.
1905 Blackwood, J. D., 5346 Wayne Avenue, Germantown.
1905 Bland, P. B., 1840 South Broad Street.

ELECTED
1893 Bochroch, Max H., 937 North Eighth Street.
1892 Boger, John A., 2213 North Broad Street.
1898 Boston, L. Napoleon, 1531 South Broad Street.
1893 Boyer, H. P., 4602 Baltimore Avenue.
1898 Brinton, Ward, 1423 Spruce Street.
1896 Brown, H. MacV., 4608 Baltimore Avenue.
1904 Brown, H. M., 4608 Baltimore Avenue.
1895 Brubaker, A. P., 105 North Thirty-fourth Street.
1893 Bryan, J. Roberts, 4200 Chestnut Street.
1901 Buckley, A. C., 1705 North Fifteenth Street.
1887 Burr, Charles W., 1327 Spruce Street.

1905 Cadbury, W., 4044 Chestnut Street.
1907 Cadwalader, W. B., 1710 Locust Street.
1906 Campbell, J. M., 655 North Twelfth Street.
1902 Carncross, H. L., 721 Pine Street.
1903 Carnett, J. B., 318 South Fifteenth Street.
1893 Carpenter, H. B., 1805 Spruce Street.
1902 Carpenter, H. C., 1805 Spruce Street.
1897 Carpenter, J. T., Jr., 1624 Walnut Street.
1887 Cattell, H. W., 3709 Spruce Street.
1906 Chandler, Swithin, 2010 Chestnut Street.
1898 Chestnut, J. E., 1817 Frankford Avenue.
1899 Clark, John G., 2017 Walnut Street.
1866 Cleemann, Richard A., 2135 Spruce Street.
1898 Coates, George M., 334 South Nineteenth Street.
1900 Codman, C. A. E., 320 South Forty-second Street.
1905 Cope, Thomas A., 6504 Germantown Avenue.
1872 Cohen, J. Solis, 1824 Chestnut Street.
1902 Cohen, M. Solis, 4110 Parkside Avenue.
1883 Cohen, S. Solis, 1525 Walnut Street.
1896 Coley, Thomas Luther, 257 South Twenty-first Street.
1907 Conaway, W. P., 1723 Pacific Avenue, Atlantic City, N. J.
1890 Coplin, W. M. L., 1529 South Broad Street.
1901 Craig, F. A., 732 Pine Street.
1903 Crampton, G. S., 251 South Seventeenth Street.
1906 Crispin, E. L., Pennsylvania Hospital.
1899 Cruice, John M., 1815 Spruce Street.
1901 Cryer, M. H., 1420 Chestnut Street.
1906 Cullinan, H. M., 1953 Locust Street.
1904 Cummins, W. T., 1111 Spruce Street.
1898 Currie, Thos. R., 113 East Cumberland Street.
1871 Curtin, Roland G., 22 South Eighteenth Street.

ELECTED
1896 Da Costa, J. C., Jr., 1022 Spruce Street.
1894 Da Costa, J. Chalmers, 2045 Walnut Street.
1885 Daland, Judson, 317 South Eighteenth Street.
1857 Darrach, James, 5923 Greene Street, Germantown (O. M.).
1882 Davis, G. G., 1814 Spruce Street.
1900 Deal, J. C., 5301 Haverford Avenue.
1889 Deaver, H. C., 1534 North Fifteenth Street.
1885 Deaver, J. B., 1634 Walnut Street.
1882 Dercum, F. X., 1719 Walnut Street.
1906 Despard, D. L., 1900 Chestnut Street.
1904 Dever, Francis T., 2025 Columbia Avenue.
1907 Dintenfass, 415 Pine Street.
1905 Doland, Charles M., Pennsylvania Hospital.
1902 Dorrance, G. M., 1716 Locust Street.
1901 Dorsett, R. S., 1105 North Fortieth Street.
1894 Dougherty, S. W., 256 South Sixteenth Street.
1889 Downs, Norton, 215 West Walnut Lane, Germantown
1903 Drein, W. C., 1438 North Fifteenth Street.
1866 Duer, Edward L., 1606 Locust Street.
1907 Dugan, W. J., 2224 South Broad Street.
1876 Dulles, C. W., 4101 Walnut Street.
1900 Dye, F. H., 1830 Girard Avenue.

1896 Edsall, David L., 1432 Pine Street.
1905 Eisenhart, W. G., 1926 North Fifth Street.
1902 Ellis, A. G., 2524 North Seventeenth Street.
1900 Erck, T. A., 251 South Thirteenth Street.
1891 Eshner, A. A., 1019 Spruce Street.
1906 Evans, Clarke, 1900 Chestnut Street.
1902 Evans, J., 2014 Locust Street.

1901 Farr, C. B., 326 South Seventeenth Street.
1881 Fenton, T. H., 1319 Spruce Street.
1907 Fetterolf, George, 330 South Sixteenth Street.
1903 Fife, C. A., 318 South Fifteenth Street.
1876 Fisher, Henry M., 917 Pine Street
1907 Flick, Lawrence F., 738 Pine Street.
1903 Fox, H., 4443 Spruce Street.
1894 Fox, L. Webster, 1304 Walnut Street.
1899 Francine, A. P., 218 South Fifteenth Street.
1895 Frazier, Charles Harrison, 1724 Spruce Street.
1890 Friebis, George, 1906 Chestnut Street.
1903 Funcke, J., 1130 Spruce Street.
1885 Fussell, M. H., 189 Green Lane, Manayunk.

ELECTED
1902 Geisler, Howard D., 202 High Street, Germantown.
1870 Getchell, Frank H., 1432 Spruce Street.
1905 Gilbride, John J., 2412 North Sixth Street.
1902 Gildersleeve, Nathaniel, Laboratory of Hygiene, University of Pennsylvania.
1894 Girvin, John H., 3924 Walnut Street.
1902 Githens, T. S., 1337 Pine Street.
1898 Gittings, J. Claxton, 3942 Chestnut Street.
1899 Given, E. E. W., 2714 Columbia Avenue.
1882 Godey, H. E., N. E. corner Nineteenth and Spruce Streets.
1900 Goepp, R. M., 332 South Fifteenth Street.
1905 Goldberg, H. G., 1733 Chestnut Street.
1906 Goodman, E. H., 2035 Chestnut Street.
1905 Gordon, Alfred, 1430 Pine St.
1902 Graham, E. E., 1713 Spruce Street.
1906 Gray, R. L., 3031 North Broad Street.
1890 Grayson, C. P., 251 South Sixteenth Street.
1883 Griffith, J. P. C., 1810 Spruce Street.
1897 Gross, Wm. D., 701 North Fortieth Street.
1906 Guilfoyle, W. F., 3722 Walnut Street.
1890 Gummey, Frank B., 5418 Greene Street, Germantown.
1900 Gwyn, N. B., 23 South Twenty-first Street.

1893 Hamill, S. M., 1822 Spruce Street.
1893 Hand, Alfred, Jr., 1724 Pine Street.
1885 Hare, Hobart Amory, N. W. cor. Eighteenth and Spruce Streets.
1857 Harlan, G. C., 1700 Walnut Street (O. M.).
1890 Hartzell, M. B., 3644 Chestnut Street.
1904 Hatfield, C. J., 2008 Walnut Street.
1901 Hawke, W. W., Philadelphia Hospital.
1900 Head, J., 1500 Locust Street.
1870 Henry, Frederick P., 1635 Locust Street.
1896 Henry, John N., 252 South Sixteenth Street.
1903 Herzberg, M., 5355 Webster Street.
1880 Hewson, Addinell, Jr., 2120 Spruce Street.
1903 Hill, H. K., 1715 Spruce Street.
1899 Holloway, T. B., 1928 Chestnut Street.
1905 Holmes, E. B., 2030 Chestnut Street.
1905 Horne, S. Hamill, 1433 Walnut Street.
1905 Hosmer, C. M., 2040 Chestnut Street.
1904 Hoyt, D. M., 3604 Chestnut Street.
1882 Hughes, W. E., Fortieth and Chestnut Streets.
1904 Hume, J. E., 900 South Forty-ninth Street.

ELECTED
1901 Hunsicker, C. H., 1614 North Broad Street.
1902 Hunter, John W., 1934 Chestnut Street.

1901 Irwin, J. W., 1923 Vine Street.

1904 Jenks, Horace H., 920 Clinton Street.
1895 Jopson, J. H., 1824 Pine Street.
1898 Judson, Chas. F., 1539 Pine Street.
1899 Jump, H. D., 4634 Chester Avenue.
1898 Kalteyer, F. J., 214 South Fifteenth Street.
1901 Kane, J. A. B., 211 South Seventeenth Street.
1906 Keene, Floyd E., 334 South Sixteenth Street.
1895 Kelly, A. O. J., 1911 Pine Street.
1906 Kelly, James A., 1612 North Seventeenth Street.
1905 Kelly, Thos. C., 128 East Price Street, Germantown.
1888 Kirby, Ellwood R., 1202 Spruce Street.
1905 Klaer, F. H., 334 South Sixteenth Street.
1900 Klapp, W. P., 1716 Spruce Street.
1890 Kneass, Samuel S., The Warwick, Nineteenth and Sansom Streets.
1898 Knipe, J. C., 2035 Chestnut Street.
1901 Kohn, B., 1325 North Thirteenth Street.
1895 Krusen, Wilmer, 127 North Twentieth Street.
1892 Kyle, D. Braden, 1517 Walnut Street.

1899 Landis, H. R. M., 130 South Twenty-third Street.
1890 Laplace, Ernest, 1828 South Rittenhouse Square.
1898 Latta, Samuel W., 233 South Fourth Street.
1905 Lavenson, Ralph S., 1218 Locust Street.
1894 Leach, W. W., Eastern State Penitentiary, Medical Department.
1869 Leaman, Henry, 828 North Broad Street.
1888 Leidy, Joseph, 1319 Locust Street.
1905 L'Engle, Edward M., 132 South Twenty-third Street.
1887 Leopold, Isaac, 1520 Franklin Street.
1904 Leopold, S., 1632 Franklin Street.
1902 Levi, I. V., 1736 North Sixteenth Street.
1875 Lewis, Morris J., 1316 Locust Street.
1899 Lindauer, Eugene, 2018 North Thirty-second Street.
1886 Lloyd, James Hendrie, 3918 Walnut Street.
1898 Lodholtz, Edward, 3103 Diamond Street.
1903 Loeb, Leo, University of Pennsylvania.
1894 Loeb, Ludwig, 1421 North Fifteenth Street.
1902 Loeb, V. A., 1901 North Eighth Street.

ELECTED
1901 Longcope, W. T., 323 South Sixteenth Street.
1875 Longstreth, Morris, 1416 Spruce Street.

1896 McCarthy, D. J., 1329 Spruce Street.
1904 McClary, Samuel, 3d, 308 South Fifty-second Street.
1880 McClellan, George, 1116 Spruce Street.
1892 McFarland, J., 442 W. Stafford Street, Germantown.
1902 McGowan, J. M., 406 South Broad Street.
1894 McKee, James H., 1519 Poplar Street.
1906 McLaughlin, J. J., 1813 South Broad Street.
1905 Maier, E. G., 2242 North Broad Street.
1905 Maier, F. Hurst, 2244 North Broad Street and 1900 Chestnut St.
1902 Marshall, C. J., 2004 Pine Street.
1899 Masland, H. C., 2134 North Nineteenth Street.
1873 Meigs, Arthur V., 1322 Walnut Street.
1906 Meyers, Milton K., 2134 North Eighteenth Street.
1878 Mills, C. K., 1909 Chestnut Street.
1906 Mitchell, Charlotte B., 1707 Pine Street.
1884 Mitchell, J. K., 1730 Spruce Street.
1907 Montgomery, C. M., 256 South Fifteenth Street.
1898 Morris, Henry, 313 South Sixteenth Street.
1885 Morrison, William H., 8021 Frankford Avenue, Holmesburg, Pa.
1887 Morton, S. W., 1933 Chestnut Street.
1899 Müller, G. P., 334 South Fifteenth Street.
1906 Muschlitz, Chas. H., 3611 Spruce St.
1880 Musser, J. H., 1927 Chestnut Street.

1879 Neff, J. S., 2300 Locust Street.
1903 Nesbit, V., 908 Pine Street.
1900 Newlin, A., 253 South Thirteenth Street.
1898 Newton, R. D., 6137 Vine Street.
1902 Noble, C. P., 1509 Locust Street.
1900 Norris, Geo. W., 1530 Locust Street.

1894 O'Malley, Joseph, 2228 South Broad Street.

1893 Packard, F. R., 1836 Pine Street.
1907 Pancoast, H. K., 4238 Pine Street.
1901 Patterson, F. D., 2103 Locust Street.
[illegible] Pearson, L., Veterinary Department, University of Pennsylvania.
1903 Pemberton, R., 1953 Locust Street.
1897 Pepper, William, 1811 Spruce Street.

ELECTED
1895 Perkins, F. M., 1428 Pine Street.
1897 Peter, L. C., 1700 Oxford Street.
1902 Pfahler, G. E., 1321 Spruce Street.
1885 Piersol, G. A., 4724 Chester Avenue.
1905 Piersol, Geo. M., 1624 Pine Street.
1907 Pitfield, R. L., 5211 Wayne Avenue.
1890 Potts, C. S., 1733 Chestnut Street.
1901 Purves, G. M., 4204 Walnut Street.

1905 Radasch, H. E., 914 South Forty-seventh Street.
1904 Rahte, Walter E., 309 South Sixteenth Street.
1885 Randall, B. A., 1717 Locust Street.
1904 Reber, Wendell, 1212 Spruce Street.
1894 Reckefus, C. H., 506 North Sixth Street.
1906 Reichel, John, William Pepper Laboratory.
1907 Repplier, S. J., 328 South Sixteenth Street.
1894 Rhein, J. H. W., 1732 Pine Street.
1903 Rhein, R. D., 2016 Pine Street.
1907 Richardson, W. W., State Hospital for Insane, Norristown, Pa.
1894 Riesman, David, 1624 Spruce Street.
1891 Ring, G. O., 2012 Chestnut Street.
1904 Rivas, Damaso, corner Sixty-seventh and Vine Streets.
1876 Roberts, John B., 313 S. Seventeenth Street.
1884 Robertson, W. E., 320 South Sixteenth Street.
1901 Robinson, E. T., 1326 Pine Street.
1904 Robinson, G. Canby, Pennsylvania Hospital.
1889 Robinson, William Duffield, 2012 Mount Vernon Street.
1901 Roe, W. J., 1210 Locust Street.
1898 Rosenberger, R. C., 2330 North Thirteenth Street.
1894 Ross, George, 1721 Spruce Street.
1900 Roussel, A. E., 2112 Pine Street.
1995 Royer, Franklin B., Municipal Hospital.

1895 Sailer, Joseph, 248 South Twenty-first Street.
1905 Salus, H. W., 1118 Pine Street.
1904 Sargent, A. Alonzo, 939 Spruce Street.
1890 Sartain, Paul J., 212 West Logan Square.
1895 Schamberg, J. F., 1922 Spruce Street.
1904 Schumann, E. A., 15 Pelham Road.
1882 de Schweinitz, G. E., 1705 Walnut Street.
1893 Scott, J. A., 1834 Pine Street.
1907 Sharpless, F. C., Rosemont, Pa.

ELECTED
1902 Shields, W. G., Jr., 412 West School House Lane, Germantown.
1905 Shoemaker, Hanlan, 1618 Spruce Street.
1889 Shoemaker, Harvey, 2011 Chestnut Street.
1896 Shumway, E. A., 2007 Chestnut Street.
1899 Sinclair, J. F., 4103 Walnut Street.
1903 Singer, Benjamin L., 1914 North Eighteenth Street.
1902 Sinkler, Francis W., 348 South Sixteenth Street.
1868 Sinkler, Wharton, 1606 Walnut Street.
1901 Siter, E. H., 2038 Locust Street.
1881 Skillern, P. G., 241 South Thirteenth Street.
1903 Small, J. H., 914 South Forty-eighth Street.
1903 Smith, A. J., Medical Department, University of Pennsylvania.
1902 Somers, Lewis S., 3554 North Broad Street.
1905 Speese, John, 328 South Sixteenth Street.
1893 Spellissey, Joseph M., 110 South Eighteenth Street.
1896 Spiller, William G., 4409 Pine Street.
1904 St. John, E. Q., 1833 Chestnut Street.
1890 Stahl, B. F., 1727 Pine Street.
1901 Stanton, W. B., 732 Pine Street.
1893 Steele, J. D., Fortieth and Locust Streets.
1904 Stellwagon, Thomas C., Jr., 1121 Spruce Street.
1889 Stengel, Alfred, 1811 Spruce Street.
1889 Stevens, Arthur A., 314 South Sixteenth Street.
1896 Stewart, Alonzo H., 252 North Twelfth Street.
1899 Stout, G. C., 1611 Walnut Street.
1905 Stout, Philip S., 4625 Woodland Avenue.
1884 Strittmatter, I. P., 999 North Sixth Street.
1869 Stryker, Samuel S., 3833 Walnut Street.
1894 Swan, John M., 3713 Walnut Street.

1899 Talley, J. E., 1927 Chestnut Street.
1897 Teller, Wm. H., 1713 Green Street.
1906 Thomas, B. A., 1819 Chestnut Street.
1894 Thomas, W. Hersey, 1421 North Seventeenth Street.
1902 Thornton, E. Q., 922 Spruce Street.
1902 Tracy, S. E., 1415 Walnut Street.
1897 Tucker, Henry, 2000 Pine Street.
1863 Tyson, James, 1506 Spruce Street.
1890 Tyson, T. Mellor, 1506 Spruce Street.

1900 Uhle, A. A., 1327 Jefferson Street.
1904 Ullman, J. T., 24 Carpenter Street, Germantown.

ELECTED
1894 Vandervoort, C. A., 3311 North Broad Street.
1887 Vansant, Eugene L., 1929 Chestnut Street.
1905 Van Kaathoven, J. A. A., 1715 Spruce Street.

1903 Walker, J. K., 1632 Spruce Street.
1891 Wallace, James, 1921 Chestnut Street.
1899 Walsh, J. 732 Pine Street.
1890 Warder, C. B., 1633 Spruce Street.
1903 Weisenburg, T. H., 2030 Chestnut Street.
1887 Westcott, T. S., 1833 Spruce Street.
1897 White, Courtland Y., 1808 Diamond Street.
1873 White, J. William, 1810 South Rittenhouse Square.
1901 Whiteway, Harold M., 1924 Chestnut Street.
1893 Whiting, A. D., 1523 Spruce Street.
1905 Wieder, Henry S., 2131 North Fifteenth Street.
1868 Willard, De Forest, 1901 Chestnut Street.
1898 Willson, R. N., 1708 Locust Street.
1906 Wilson, J. D., Jefferson Medical College.
1869 Wilson, James C., 1509 Walnut Street.
1907 Wilson, Oscar H., 5128 Spruce Street.
1891 Wilson, Samuel M., 1517 Arch Street.
1901 Winsor, Henry, in care of Winsor & Co., Piers 18 and 20, South Delaware Avenue.
1900 Wister, J. W., 5430 Germantown Avenue.
1907 Wolf, Henry F., 1804 Green Street.
1890 Wood, A. C., 128 South Seventeenth Street.
1898 Wood, George B., 129 South Eighteenth Street.
1906 Wood, Harold B., 5038 Pine Street.
1865 Woods, D. Flavel, 1501 Spruce Street.
1899 Worden, C. B., 4208 Walnut Street.

1902 Zimlick, A. J., 702 East Chelten Avenue.
1895 Zimmerman, Mason W., 1522 Locust Street.

NON-RESIDENT MEMBERS.

Alburger, Henry R., Bloomington Indiana.
Ball, M. V., Warren, Pa.
Biddle, Clement, on sea duty.
Biggs, M. H., Rutherford, N. C.
Breinig, P. B., Bethlehem, Pa.
Carter, W. S., Galveston, Texas.
Cerna, D., Galveston, Texas.
Chrystie, Walter, Bryn Mawr,'Pa.
Coca, A. F., University of Pennsylvania.
Davisson, Alexander H., Ardmore, Pa.
Dock, George, Ann Arbor, Mich.
Edwards, W. A., San Diego, Cal.
Egbert, Joseph P., Wayne, Delaware County, Pa.
Fenn, William B., Denver, Col.
Fox, J. M., Torresdale, Pa.
French, Samuel, Plymouth, Pa.
Gaylord, H. R., Buffalo, N. Y.
Gerson, T. P., 1621 Ingraham Street, Los Angeles, Cal.
Gilliland, S. H., Marietta, Pa.
Hamaker, W. D., Meadville, Pa.
Hamann, C. A., 517 Euclid Avenue, Cleveland, Ohio.
Harris, H. F., Atlanta, Georgia.
Harrison, W. H., Harrisburg, Pa.
Hatch, John L., 2010 Fifth Avenue, New York City.
Hickman, W. A., 612 Pacific Avenue, Atlantic City.
Hileman, J. B., Altoona, Pa.
Hitchens, A. P., Glenolden, Pa.
Holder, C. A., Colorado Springs, Col.
Howard, F. H., Williamstown, Massachusetts.
Hunt, J. R., 102 East Fifty-seventh Street, New York.
Jamar, John H., Elkton, Md.
Jarrett, Henry, Broadway and Cherry Streets, Camden, N. J.
Kennedy, L. F., 303 Mauch Chunk Street, Pottsville, Pa.
Kiefer, Charles, United States Army.
Kinyoun, J. J., Glenolden, Pa.
Lincoln, C. W., 314 East Lancaster Avenue, St. David's, Pa.
Lincoln, W. R., Cleveland, Ohio.

Ludlam, S. D., Friends' Asylum, Frankford, Pa.
Lukens, G. T., Fifth Avenue and Fayette Street, Conshohocken, Pa.
McConnell, G., 5012 Parkside Avenue, St. Louis, Mo.
Muhlenberg, Frank, Reading, Pa.
de Nancrède, C. B. G., Ann Arbor, Mich.
O'Reilly, C., Strafford, Pa.
Osler, William, University of Oxford, England.
Pearce, Richard M., New York State Board of Health, Albany, N. Y.
Pease, H. D., Buffalo, N. Y.
Pfouts, G. B., Morris Plains, N. J.
Powell, W. M., 122 West Minor Street, West Chester, Pa.
Rahter, C. A., Harrisburg, Pa.
Ranck, E. M., 107 Main Street, Natchez, Miss.
Ravenel, M. P., University of Wisconsin.
Reynolds, W., 27 South Indiana Avenue, Atlantic City.
Richardson, W. W., State Hospital for Insane, Norristown, Pa.
Robins, Albert, Wilmington, Del.
Schreiner, E. R., U. S. Army.
Sharpless, William T., 100 South Church Street, West Chester, Pa.
Slifer, Henry F., North Wales, Pa.
Smith, Henry Field, Odessa, Del.
Sommers, Henry J., State Hospital for Insane, Norristown, Pa.
Stadelman, Eugene, "Magistral," Maria Del Oro, Dgo., Mex.
Stiles, G. A., Conshohocken, Pa.
Stubbs, R. P., Wilmington, Delaware.
Taylor, A. E., University of California, San Francisco, California.
Taylor, L. H., Wilkesbarre, Pa.
Toulmin, H., Haverford, Pa.
Walter, Georgianna, Christiana, Pa.
Wells, G. M., Wayne, Delaware County, Pa.
Wetherill, R. B., Lafayette, Ind.
White, Frank, Elwyn, Pa.
Williams, H. L., Minneapolis, Minnesota.
Wilmarth, A. W., State Home for the Feeble-minded, Chippewa Falls, Wisconsin.
Yates, J. L., Ellis Avenue, Chicago, Ill.
Ziegler, J. L., Mt. Joy, Pennsylvania.

CORRESPONDING MEMBERS.

ELECTED

1898 Cornil, V., Faculté de Médecine, Paris, France.

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The Nature and the Lesions of Cirrhosis of the Liver, with Special Reference to the Regeneration and Rearrangement of the Liver Parenchyma.

BY A. O. J. KELLY, M.D.

THE study of cirrhosis of the liver has been approached from several points of view, etiologic, anatomic, and clinical; but since the disorder was first described by Vesalius especial interest has centered in the obvious and most conspicuous feature of the lesions —the fibrosis—so much so, indeed, that the term "cirrhosis," first employed by Laënnec to describe the yellowish (κιῤῥός),, hobnails," which he regarded as new-growth, has by a curious transference of meaning become almost inseparable from, with some writers practially identical with, the sclerotic process, and indeed by the ill-nformed its meaning is not infrequently expanded so as to include sclerotic and fibrotic processes in other organs. As contrasted with the conspicuous fibrosis the changes in the parenchyma of the liver in cirrhosis have received comparatively scant attention. They are commonly, though, of course, not universally, looked upon as progressively and continuously degenerative or atrophic, usually subsidiary in importance, and secondary to, consequent upon, the changes in the interstitial tissue. It is true, however, that the so-called pseudo-bile-ducts, or canaliculi, present in many cases of cirrhosis, are usually nowadays looked upon as evidences of a regenerative process; that the liver cells are further capable of quite extraordinary regeneration is now well known in consequence of experimental investigation and the study of the changes following acute yellow atrophy and allied processes, and such regeneration is generally recognized in the adenoma-like formations that occur under diverse circumstances; but that any noteworthy regeneration of the liver cells is a part of ordinary cirrhosis is not commonly taught.

The recent studies and several communications of Kretz,[1] however, throw considerable light upon the nature of cirrhosis, and the still more recent communications by MacCallum[2] and Böstrom,[3] as well as the results of some experimental work, notably recently by Pearce,[4] lend confirmation to his views. My own work, which in some particulars is merely confirmatory of the already published work of Kretz and of MacCallum, is based upon a study of the thirty cases of cirrhosis, and of many other cases of disease of the liver that have come to necropsy at the German Hospital, Philadelphia, during the last eight years; certain clinical data of patients treated in the German Hospital during the last fifteen years, in whom a diagnosis of cirrhosis of the liver was made—for permission to use which I am much indebted to Dr. James C. Wilson, physician-in-chief to the German Hospital; several cases of cirrhosis observed on Dr. Musser's service in the University Hospital, for permission to utilize which I am much indebted to Dr. Musser; several cases observed on my own service at St. Agnes' Hospital; many of Professor Kretz's preparations;

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[1] Ueber Lebercirrhose, Wien. klin. Woch., 1900, vol. xiii. p. 271; Lubarsch und Ostertag's Ergebuisse der allg. Path. und path. Anat., 1904, vol. viii. p. 473 (Bericht über das Jahr., 1902); Verhandl. der deut. path. Gesellschaft, 1904, vol. viii. p. 54; International Clinics, 1905, 15th series, vol. iii. p. 289.

[2] Regenerative Changes in Cirrhosis of the Liver, Jour. Amer. Med. Association, 1904, vol. xliii. p. 649.

[3] Lebercirrhose, Deut. med. Woch., 1905, vol. xxxi. p. 167.

[4] A paper on Experimental Cirrhosis of the Liver, read at the meeting of the American Association of Pathologists and Bacteriologists in Chicago, April, 1905, and to be published in the Journal of Experimental Medicine.

and other pieces of tissue from unusual cases, for which I am indebted to several friends, notably Dr. W. F. Hamilton, of Montreal, Dr. Allen J. Smith, of Philadelphia, Dr. W. M. L. Coplin, of Philadelphia (spontaneous cirrhosis in dogs), etc. I shall consider (1) the structure of the liver in so far as it has a bearing upon the changes in cirrhosis; (2) the changes in the parenchyma of the liver in cirrhosis; (3) the changes in the connective tissue in cirrhosis; and (4) the permissible deductions with regard to the nature of cirrhosis that may be drawn from the foregoing.

THE STRUCTURE OF THE NORMAL LIVER. Although it is largely supererogatory at this day to discuss the structure of the normal liver, a clear conception of the cirrhotic process is best attained by bearing in mind that, as recognized years ago by Hyrtl[1] and recently especially emphasized by Kretz, the liver is not made up of acini in an acceptable sense. While the physiologic unit of the liver is that collection of cells drained by a radicle of the bile-duct, this unit is scarcely delimitable anatomically, although Sabourin[2] has made an attempt to do so; nor are the so-called acini, or lobules, cross-sections of which surrounded by connective tissue form such a conspicuous feature of microscopic sections, of such simple structure as at first sight appears. Study of the liver in serial sections and its reconstruction show that the liver parenchyma does not form isolated acini, or lobules, everywhere surrounded by connective tissue, but that what appear to be acini are merely cross-sections of liver cells arranged as a mantle about the numerous dendritic ramifications of the hepatic vein, and that this mantle is nowhere discontinuous, forming, on the contrary, a continuous whole, everywhere connected, particularly at the points of junction of the sublobular, lobular, and lobar veins. The intimate relationship that the liver cells structurally bear to the hepatic vein is further shown by the radial disposition of the cells about the branches of this vein, the so-called central veins.

Pervading and filling the spaces left between the arborescent ramifications of the hepâtic vein with its cell mantles are the radicles of the portal vein, accompanied by the hepatic artery and the bile-ducts, all supported by connective tissue (the capsule of Glisson), sparse in some places, more abundant in others; but such is the arrangement of the intertwinings of the "portal tree" and the "hepatic tree" that the finest ramifications of the one are everywhere separated from those of the other by a collection (mantle) of liver cells.

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[1] Lehrbuch der Anatomie des Menschen, 1873, 12te Aufl., p. 936.

[2] Etude compare du foie de l'homme et du foie du cochon, Revue de Med., 1901, vol. xxi. p. 384.

As distinguished from most other organs the liver has two sources of blood supply—the portal vein and the hepatic artery—which commingling form a plexiform capillary network, in the meshes of which the liver cells are arranged. Ultimately the capillaries unite again to form the radicles of the hepatic vein—the rectilinear veins of Sabourin, which empty into the so-called central veins. The circulation within the liver, which is not only interesting in itself but of much importance in connection with certain features of cirrhosis, has recently been studied attentively by Opie.[1] It has long been known, and Opie directs renewed attention to the fact, that one of the important characteristics of the liver is its susceptibility to variations in blood pressure, saying: "The portal vein, hepatic artery, and hepatic vein are in such free communication that the entire lobule can be injected from any one of these vessels. Hence artificial injections do not define the intralobular distribution of the portal and arterial blood, for doubtless differences of venous and arterial pressures have a part in determining peculiarities of the circulation within the lobule." Opie's experimental studies led him to the conclusion "that both the hepatic artery and portal vein pour their blood into the periphery of the lobule, and here the influence of the arterial blood pressure is most strongly felt. When foreign material reaches the liver by the portal vein it is washed from the peripheral zone by the arterial blood, and tends to be deposited in a middle zone, where the influence of the opposing circulation is less strongly felt. Hence it is not improbable that toxic substances capable of causing necrosis of the hepatic cells, brought to the liver by the portal vein, might first exert their effect upon cells within a midlobular zone. The periphery of the lobule, moreover, is supplied with arterial blood, and is perhaps for this reason less susceptible to injurious agencies."

Changes in the Parenchyma of the Liver. If we examine attentively the parenchyma of the liver in a moderately advanced or well-advanced case of cirrhosis certain noteworthy deviations from the normal become apparent: (*a*) Changes in the size of the lobules; (*b*) changes in the shape and configuration of the lobules; (*c*) changes in the arrangement of the liver cells; (*d*) degenerative or atrophic and hyperplastic changes in the liver cells, and (*e*) changes in the vascular arrangement and supply.

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[1] Zonal Necrosis of the Liver, Jour. Medical Research, 1904, vol. xii p. 147.

Changes in the Size of the Lobules. One of the patent and noteworthy features of the lesions of cirrhosis is the marked variation in size of the "granules" or "hobnails," which not only vary considerably in size in different cases, but also in the same case in different parts of the liver, some being notably smaller, others notably larger than the lobules of the normal liver. Long identified as the analogue of the normal liver lobule, it is now well known that many of them are made up of several lobules or of the remains of several lobules; but it is important to bear in mind that some of them are really single lobules, departed, however, somewhat from the normal. The question of the size of these lobules has recently been studied attentively by Kretz, MacCallum, etc.

Changes in the Shape of the Lobules. With the central vein as a point of departure, we find that, as already stated, the lobules are roundish-polygonal in shape, their long axis being in the direction of the central vein and their cross-sections roughly rounded, and that the veins are in reality central—that is, surrounded on all sides by an even thickness or mantle of cells. In diagonal or tangential sections of lobules this is not so apparent, and the picture is altered where several lobules join or where the liver cells vary somewhat their course to form the continuous mantle, especially about the junctions of sublobular and lobular veins. In cirrhosis there is a notable departure from this shape and configuration. Many of the lobules are no longer rounded, but quite irregular in transverse section. Many of the cell mantles no longer surround the central veins equally on all sides, but very unequally, so that many central veins are situated eccentrically in a more or less misshapen lobule. Many so-called lobules have no central veins at all (and are not tangential sections of otherwise normally arranged lobules). Certain lobules (or so-called lobules, usually remains of several) have two, three, four or more central veins, and often the central vein may be seen in the adjacent interlobular connective tissue. Thus we ascertain that the mantle of cells covering a central vein varies much in thickness in different regions (transverse planes), sometimes exposing, sometimes covering the vein to a greater or less extent; and that, though isolated collections of liver cells—that is, collections devoid of central veins—do occur, some supposedly isolated collections are merely sections of more or less irregularly proliferating dendritic branches of what may be called the parent stem or mantle covering a single central vein.

Changes in the Arrangement of the Liver Cells. A conspicuous feature of the normal liver lobule is the radial arrangement of the liver cells about the central vein. In cirrhosis, although this arrangement is preserved to some extent, in many places its partial or complete absence is noteworthy. The architecture of the lobule has become altered so that the cells are arranged irregularly, in parallel rows, etc. This rearrangement of the liver cells is quite as well marked in many of the lobules that have a central vein as in those collections of cells entirely devoid of central veins.

Degenerative or Atrophic and Hyperplastic Changes in the Liver Cells. The degenerative and atrophic changes in the liver cells in cirrhosis—simple atrophy, parenchymatous degeneration, fatty degeneration, fatty infiltration, pigmentary infiltration, etc.—are a part of common knowledge and for the moment need not be further discussed. It is important, however, with a view to the correct interpretation of the lesions, to bear in mind that many cells at the periphery of lobules (or so-called "hobnails") in immediate contiguity to wide bands of connective tissue are by no means atrophic, even in fairly well-advanced cases; on the contrary, it is really noteworthy that whereas, *a priori*, in conformity with prevailing opinions, compression atrophy of these cells should be expected, and is indeed often commented upon, the cells that should exhibit this alteration most markedly—that is, those at the periphery of the lobule—often present an unusually plump and healthy appearance, and cannot, therefore, have been unduly compressed.

Special attention, however, should be directed to the evidences of hyperplasia of the liver cells that are readily found in almost every cirrhotic liver, even in far advanced cases. Mitoses, it is true, are rarely encountered in advanced cases, largely in consequence of the nature of the process, the advanced stage at which the examination is generally undertaken and the length of time after death that the liver is obtained, time sufficient for the completion of any mitoses present at death. That many of the liver cells, however, are newly formed is quite apparent from their large, clear, and plump appearance, their rounded (rather than polygonal) outline, the presence of two or more nuclei, and the absence of fat and of pigment from their protoplasm. And what is especially noteworthy is that these cells, sometimes small collections of them, are situated amidst other liver cells, normal in size and outline, provided with only a single nucleus each (though sometimes with two nuclei, which is quite normal), and the protoplasm of which is normally pigmented and contains fat. These newly formed cells are usually found at the periphery of a lobule. Sometimes they make up a larger or smaller sector of a lobule; sometimes they seem to have compressed the older cells of their immediate vicinity, and sometimes small collections of them are found completely surrounded by wide bands of connective tissue, where by their generally plump and healthy appearance they convict the connective tissue of exerting less constrictive force than they themselves expansive force. The sector of a lobule sometimes made up of these cells, serves in some cases to restore more or less completely the normal outline of the lobule—that is, of the mantle of cells covering a central vein—in which event a part of the mantle of cells consists of such newly formed cells arranged irregularly and a part of older cells arranged radially. In other cases this cellular hyperplasia has occurred in such a manner that the central vein is more or less exposed on one side and on the other covered with a mantle of cells often twice or thrice the normal thickness.

In acute and subacute, or what may be called recurring cases, mitoses are occasionally encountered (doubtless they would be more frequently encountered were our methods of investigation better thereto adapted), and necrotic and hyperplastic changes may be found side by side in the one lobule.

A characteristic feature of almost all cases of cirrhosis, more conspicuous, however, in some cases than in others, is the bile-ducts or so-called pseudobiliary canaliculi, the nature and origin of which has for a long time occasioned much discussion. Doubtless the great increase of these structures in cirrhosis, as contrasted with the normal liver, is relative only and due in part, but only in small part, to mutual approximation of already existing bile-ducts occurring in consequence of loss of the liver tissue, but that most of them are newly formed is generally conceded, and is quite apparent from their excessive number and the evidences of active proliferation (mitosis) that they commonly exhibit. Their origin has not been determined definitely for all cases. Dispensing for the time being with a detailed discussion of the question, it seems quite certain that some, at least, of them result from proliferation of previously existing bile-ducts; on the other hand, since they are found in a wide variety of disorders, such as all forms of cirrhosis, acute yellow atrophy in the neighborhood of hydatid cysts, tubercles, gummas, etc., in other words, in diseases alike only in that they destroy liver tissue; since they differ from normal bile-ducts in the absence or relative paucity of encircling elastic tissue; since they have been found by Ackermann and others to be directly continuous with liver cells, and since in cases in which the liver cells have been much destroyed they are found in large numbers in what may be interpreted as the remains of the skeleton of the lobule, we are quite warranted in the opinion that they may result from proliferation of the liver cells themselves, constituting in this event a reversion to a less highly specialized type of structure. The important fact only that I wish to point out in this connection is the histogenetic equivalence of the liver cells and the epithelium of the bile-ducts and the fact that proliferative changes of the liver parenchyma is a conspicuous feature of common cirrhosis.

Changes in the Vascular Arrangement and Supply. Reference has already been made to the fact that the central veins are situated eccentrically in certain more or less distorted and rearranged lobules, that they may be found at the edge of certain lobules or remains of lobules, and even in the interlobular connective tissue,and that certain islets of liver tissue are totally devoid of central veins. Another noteworthy feature is that the central veins appear to have diminished in number in the liver as a whole. Corresponding to the smaller size of many of the cirrhotic livers and the associated loss of the liver parenchyma, the central veins in certain regions sometimes exhibit a mutual approximation, which, however, varies much in different livers and in the same liver in different places. In some regions where considerable hepatic cell hyperplasia has occurred they are often quite widely separated; but were the central veins not diminished in number in the liver as a whole we should expect to find in a small so-called atrophic cirrhotic liver a relative increase in the number of central veins in a given square surface as compared with a square surface of similar size in a normal-liver—which, however, is not the case. The absolute lessening of the number of central veins becomes further evident when we recall the many islets of liver tissue (likely at first sight to be interpreted as more or less distorted lobules) entirely devoid of central veins.

Confirming the view that a number of the central veins have disappeared, we may sometimes find in sections happily cut through the desired plane bulbous and distorted side branches of the sublobular and lobular veins. Furthermore Kretz, who has studied attentively the circulation in the cirrhotic liver, seems conclusively to have proved by means of injected and macerated preparations that the finer ramifications of the hepatic vein are fewer than in the normal liver, that the sublobular and lobular branches are more tortuous and in some place's larger and thicker, and that they have attached to them bulbous and distorted side branches, representing, according to him, the atrophic remains of central, sublobular, and lobular veins persisting after the disappearance of the related parenchyma.

CHANGES IN THE CONNECTIVE TISSUE. A study of the connective tissue in almost any well-marked cirrhotic ("coarsely granular") liver shows that it is made up of several sorts of tissue: (1) Some of it is unquestionably newly formed; of this there is no doubt, the debatable point being as to its nature and genesis; (2) some of it is the tissue originally between the lobules—the connective tissue of Glisson's capsule; and (3) some of it is the collapsed and otherwise altered reticulum of certain liver lobules, the cells of which have disappeared, evidently degenerated by some influence and subsequently removed.

As regards the newly formed tissue, its nature and distribution have been studied by a large number of investigators, and little that is new can be added to what is common knowledge. It has been demonstrated by divers methods of investigation, including the use of Weigert's elastica stain, Mallory's connective-tissue and reticulum stain, digestion with pancreatin, etc., that the normal liver contains three kinds of connective tissue: (1) White fibrous tissue, present in the liver capsule and in large amount in the interlobular spaces; (2) elastic tissue, found chiefly about the bloodvessels, to a less extent about the bile-ducts and in the liver capsule, and to a very slight extent in and about the walls of the central veins; and (3) reticulum; according to Mall[1] "a great share of the tissue accompanying the interlobular vessels and all that about the intralobular is reticulated. The peritoneal surface may be viewed as a thickening of the reticulum intermixed with some white fibres."

Whereas formerly the fibrosis of cirrhosis was generally thought to consist almost if not quite exclusively of white fibrous tissue, the studies of Hohenemser,[2] Melnikow-Raswedenko,[3] Flexner,[4] McIntyre,[5] Oliver,[6] and others have shown us, and anyone can readily demonstrate that in reality it consists of all the connective tissues of the normal liver—pathologically altered, it is true. The most conspicuous change is the great increase in the elastic tissue—probably more or less intimately related to the great increase in the capillaries derived from arterioles; this elastic tissue not only makes up a large part of the fibrous bands between the lobules, but it is also found to some extent within the lobules, and occasionally a very small amount of it is found about or in the immediate neighborhood of the central veins. A not inconsiderable part of the fibrosis is made up of reticulum—not only the reticulum normally between the lobules, but also the intralobular reticulum—that remaining after the liver cells have degenerated and been removed. This collapsing intralobular reticulum may be quite readily distinguished in tolerably early cases; later, however, when it has become a part of the interlobular fibrosis it can scarcely be recognized as a distinct entity. I believe that Flexner is quite correct in the opinion that the changes in the reticulum in cirrhosis constitute an hypertrophy rather than a hyperplasia of the fibrils.

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[1] Reticulated Tissue and its Relation to the Connective-tissue Fibrils. Johns Hopkins Hospital Reports, 1896, vol. i. p. 171.

[2] Ueber das Vorkommen von elastischen Fassern bei cirrhotischen Processen der Leber und Niere, Virchow's Archiv, 1892, vol. cxl. p. 192.

[3] Histologische Untersuchungen über das elastische Gewebe in normalen und pathologisch veranderten Organen, Ziegler's Beiträge, 1899, vol. xxvi. p. 546.

[4] The Nature and Distribution of the New Tissue in Cirrhosis of the Liver. University Medical Magazine, 1900-1, vol. xiii. p. 613.

[5] Some Points in the Formation of Connective Tissue in the Liver, Glasgow Medical Journal, 1901, vol. lv. pp. 341, 415.

[6] Elastic Tissue in Cirrhosis of the Liver. Transactions of the Chicago Pathological Society, 1901-3, vol. v. p. 96.

The distribution of the connective tissue in cirrhosis has long been the subject of much and more or less fruitless discussion; and the many classifications based thereupon have not tended to clarify any of the obscurity connected with the subject. Multilobular, monolobular, and pericellular (as well as certain more or less synonymous terms, such as annular, circumlobular, unilobular, interlobular, extralobular, intralobular, perilobular, intercellular, etc.) are in common use, and are said to be descriptive of special types of the disease. Without entering upon a detailed discussion of the question at the present time I may point out that while one or the other of these varieties of distribution of connective tissue may appear to predominate in certain cirrhotic livers, all varieties are much more likely to be encountered in the one liver; and while so-called "hypertrophic" or biliary cirrhosis, as contrasted with so-called "atrophic" cirrhosis, is usually characterized by less interlobular fibrosis and an earlier and a finer intralobular fibrosis, it is frequently impossible from a mere microscopic inspection of a section of a cirrhotic liver to state to which type of the disease it belongs. Assuredly in the advanced stages the lesions tend to become very much alike. The difficulty is overcome by some writers who postulate so-called "mixed" cases.

THE NATURE OF CIRRHOSIS. Endeavoring to interpret the foregoing lesions we find that the most noteworthy feature is the complete rearrangement of the architecture of the liver parenchyma. In consequence of some cause or causes larger or smaller portions of numerous liver lobules have been destroyed, many liver lobules have been destroyed entirely—whence the necrotic changes and the skeleton of the reticulum remaining after removal of the cells that are apparent in the early stages, and the eccentric and otherwise irregular situation of many central veins (the variations in size and outline of the cell mantles) and the complete disappearance of other central veins that are apparent in the advanced stages of the disease. Furthermore, evidences of regeneration and hyperplasia of the liver cells are quite apparent—in the general appearance of many of the cells themselves, in their irregular arrangement in parallel rows, etc. (as contrasted with the normal radial arrangement), in the large hyperplastic lobular (so-called adenomatous) masses, in the irregular dendritic ramifications of liver cells with a peculiar vascularization and entirely devoid of central veins, in the pseudobiliary canaliculi, etc. Although evidences of secondary atrophy of the liver cells are by no means wanting, especially in advanced cases, the peripheral cells of many of the lobules in early cases, but often also in well-advanced cases, exhibit no evidences of compression atrophy whatever—being plump and well formed and manifesting therefore more expansive force than the surrounding connective tissue constricting force; some of the small islets of liver tissue containing central veins, since their peripheral cells exhibit no evidences of compression, must have resulted from degeneration and subsequent regeneration of the liver tissue; and some of the small islets devoid of central veins, since they exhibit no evidence of peripheral compression nor of capillary stasis, cannot have resulted from sequestration of a part of a lobule by invading connective tissue, but must represent regenerated liver tissue. The parenchyma of the liver in cirrhosis, then, consists not only of remnants of the original parenchyma, but also and in large part of regenerated liver tissue that differs from normal liver tissue in that it does not reproduce its typical architecture nor its relation to the bloodvessels—the capillaries and the central veins.

That the liver is capable of this really remarkable regeneration has been amply proved—especially by Ponfick,[1] von Podwyssozki,[2] von Meister,[3] and others, particularly Pearce[4] recently, who have studied regeneration of the liver experimentally; by Marchand,[1] Meder,[2] Stroebe,[3] Barbacci,[4] Mertens,[5] MacCallum,[6] and others who have studied the regenerative lesions following acute yellow atrophy; by the many observers (a good collective list of whom in given by Barbacci) who have studied the adenoma formations in the liver; and by Kretz,[7] Greco,[8] MacCallum,[9] and Böstrom,[10] who have studied the regenerative changes in cirrhosis.

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[1] Experimentelle Beiträge zur Pathologie der Leber. Virchow's Archiv, 1889, vol cxviii. p. 209; 1890, vol. cxix. p. 193; 1895, vol. cxxxviii. (sup. Heft) p. 81.

[2] Experimentelle Untersuchungen über die Regeneration der Drusengewebe, I. Theil, Lebergewebe, Ziegler's Beiträge, 1886, vol. i. p. 259.

[3] Ueber die Regeneration der Leberdrüse nach Entfernung ganzer Lappen, Centralblatt f. allg. Pathologie und path. Anatomie, 1891, vol. ii. p. 961.

[4] Unpublished paper on Experimental Cirrhosis of the Liver previously referred to.

The present is not the time to discuss these regenerative changes in detail, and I must content myself with pointing out that the changes found in cirrhosis when compared with those found, for instance, by Ponfick in experimental hypertrophy of the liver, are found to be identical; that is, for a short time after removal of a portion of the liver mitoses are quite abundant, but later the new-formed liver tissue partakes of the characters of the liver cells in cirrhosis that I have already mentioned—large, clear, plump cells with rounded outline, containing two or more nuclei, devoid of fat and pigment, and occurring often in the midst of other cells differing in no way from the common liver cells (smaller, usually polygonal, with a single nucleus, normally pigmented and containing fat, and sometimes even compressed by the newly formed cells).

The nature of the fibrosis in cirrhosis has long engaged the attention of pathologists whether it is an inflammatory or a replacement fibrosis is still a matter of discussion. Although the question may not be definitely decided offhand, there are many facts which suggest that the prevailing opinion that the cause of cirrhosis, whatever it may be, engenders a primary overgrowth of connective tissue is not correct.

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[1] Ueber Ausgang der acuten Leberatrophie in multiple knotige Hyperplasia, Ziegler's Beiträge, 1895, vol. xvii. p. 206.

[2] Ueber acute Leberatrophie mit besonderer Berücksichtigung der dabei beobachteten Regenerationserscheinungen, Ziegler's Beiträge, 1895, vol. xvii. p. 143.

[3] Zur Kenntniss der sogenannten acuten Leberatrophie, Ziegler's Beiträge, 1897 vol. xxi. p. 379.

[4] Ueber Ausgang der acuten Leberatrophie in multiple knotige Hyperplasia, Ziegler's Beiträge, 1901, vol. xxx. p. 49.

[5] Lesions anatomiques du foie du lapin au cours de l'intoxication chronique par le chloroform et par l'alcohol, Archives international du pharmacodynamie, vol. ii. p. 127 (quoted by Kretz).

[6] Regenerative Changes in the Liver after Acute Yellow Atrophy, Johns Hopkins Hospital Reports, 1903, vol. x. p. 375.

[7] Loc. cit.

[8] Ueber Reproduction der Leber bei Cirrhose, Centralblatt f. allg Pathologie und path. Anatomie, 1898, vol. ix. p. 371 (abstracted from La Riforma Medica, 1897, vol. iii.).

[9] Regenerative Changes in Cirrhosis of the Liver, Jour. Amer Med. Assoc., 1904, vol. xliii. p. 649.

[10] Loc. cit.

I have just mentioned certain facts that show that the lesions of the parenchyma in cirrhosis cannot with reason be regarded as secondary to (dependent upon) changes in the connective tissue—since no connective-tissue change with which we are acquainted is capable of causing the noteworthy rearrangement of the architecture of the liver so characteristic of cirrhosis, and as a matter of fact the liver parenchyma, even in many advanced cases, exhibits a notable absence of compression atrophy—a change that is so conspicuous, for instance, about a growing metastatic carcinomatous nodule in the liver.

As is well known, there is a disposition among pathologists during recent years to separate from the purely inflammatory conditions certain fibroses of which the fibroid heart, the chronic granular and arteriosclerotic kidney, certain so-called senile fibroses, sclerosis of the nervous system, and cirrhosis of the liver are conspicuous examples The scleroses of the nervous system are now almost universally believed to be examples of replacement fibrosis—hypertrophy and hyperplasia of the neuroglia to replace lost or destroyed nervous elements; in the fibroid heart, in many if not all cases, the cardiac muscle has degenerated in consequence of deficient nutritive supply or other cause, and becomes replaced by fibroid connective tissue; and other examples of such replacement fibrosis are found in pseudo-hypertrophic muscular paralysis and the atrophy of certain fetal structures at or shortly after birth. There is considerable evidence that the fibrosis of cirrhosis also is of the same nature—at least in part. The lesions of acute inflammation are scarcely if ever encountered (in view of the chronicity of the process this excites little comment), and when found they are not infrequently due to some complication; the changes in the reticulum are, as suggested by Flexner, hypertrophic rather than hyperplastic, and may be explained by recourse to Ribbert's theory of tissue tension; the new tissue as a rule is unusually rich in intercellular substance, as contrasted with cells; and many of the cells are doubtless only evidences of the effort on the part of nature to remove effete matter—necrotic liver cells. On the other hand, we cannot deny that a poison or other etiologic factor capable of causing necrosis of the liver cells may also be capable of setting up inflammatory phenomena in the interstitial tissue, although the parenchymatous cells are probably more susceptible to injurious influences; and in other cases the necrotic liver cells, being foreign bodies, act as a source of irritation, whence it is likely that if the fibrosis is largely a replacement fibrosis in some cases, in other cases it is both a replacement and an inflammatory fibrosis.

As regards the nature of cirrhosis then I may say with Kretz that it is a chronic focal or localized, recrudescing degeneration and partial destruction of the liver parenchyma attended by marked regenerative phenomena on the part of the liver cells leading to complete transformation of the architecture of the liver and followed by fibrosis. It is not a primary interstitial hepatitis, the changes in the connective tissue being altogether secondary in importance and sequence, probably in large part a replacement fibrosis to fill up potential lacunæ left by degenerated liver cells, and probably in some cases at least partly inflammatory. In consequence of the activity of some poison or other etiologic factor larger or smaller areas of the liver tissue, that is, of the cell mantles about the central veins, become necrotic and are removed—whereby the central veins become more or less uncovered, thus on cross-section appearing eccentrically situated in more or less misshapen lobules; in some cases in which the destruction of liver cells has been through the entire radius of the cell mantle the central vein may be entirely exposed and may even be found in the interlobular connective tissue—in which event it is very likely to be mistaken for a branch of the portal vein. The cells destroyed are those about the periphery of the lobules—in the area of portal distribution, conforming to the fact that the etiologic factor (poison) is usually carried by the portal vein. In case the poison is carried by the hepatic artery (as seems likely in some general infections) the lesions may be somewhat diverse, in the beginning of the process at least; and it is by no means improbable (though this still awaits proof) that the differences between the common or Laënnec's cirrhosis and so-called hypertrophic cirrhosis are in part at least dependent upon the source (portal vein or hepatic artery), in part also upon the nature, of the provoking cause. Following the primary destruction of certain liver cells, the intact cells, exhibiting a remarkable regenerative capacity, attempt to replace the lost cells and sometimes succeed in restoring more or less completely the volume of the cell mantles. The cells that regenerate are those in the immediate vicinity of those that have become necrotic; that is, in the ordinary case in which the destruction is not widespread, cells toward or at the periphery of the lobule—which thus are not only most exposed to the deleterious influence of poisons carried by the circulation, but in consequence of being better supplied by arterial blood are also better adapted for repair. I am rather inclined to believe, in view of Opie's researches on the circulation within the lobules, that the primary destructive action may be exerted, at least sometimes, in the so-called midlobular zone—at all events, not immediately at the periphery; that the peripheral cells, being better supplied with arterial blood, survive when others nearer the center of the lobule succumb; and that these peripheral cells also serve as the focus of regeneration, though, of course, the cells nearer the center of the lobule also regenerate. I am somewhat confirmed in this opinion by the characteristics and disposition of many of the pseudobiliary canaliculi which are often most numerous in the skeleton of those lobules that have been much destroyed, and seemingly grow from the periphery into the lobule, in a manner quite analogous to Ponfick's and others' descriptions of their growth into granulation tissue after destruction of the liver cells. As is now generally conceded, these pseudobiliary canaliculi sometimes grow from pre-existing bile-ducts, but as I have already pointed out and as is well known, they also develop from liver cells, which in this respect are histogenetically equivalent with the epithelium of the bile-ducts. It is also not unlikely that some of the surviving peripheral cells by proliferation give rise to certain of the hyperplastic islets of liver tissue devoid of central veins.

The continuing activity of the etiologic factor leads to a continuous or recrudescing death of certain old as well as newly formed liver cells, which in turn is followed by renewed regeneration. This continuous degeneration and regeneration ultimately lead to complete transformation of the architecture of the liver: certain lobules are entirely destroyed, others are partly or completely rearranged, some are markedly hyperplastic though tolerably well arranged, some show dendritic and other irregular proliferation, new islets of liver tissue entirely devoid of central veins appear, and what is especially important new circulatory conditions—capillary and venous—arise.

Concurrent with the degeneration of the liver cells the framework of the lobules collapses and participates in the formation of the fibrosis. This fibrosis, formed as previously described, ultimately contracts, and on the one hand causes atrophic changes in the liver cells, and on the other obstruction and obliteration of some of the interlobular and intralobular branches of the portal vein: this latter though it contributes to is not the sole cause of the ascites—other important factors being the aforementioned new circulatory conditions, especially certain noteworthy changes in the hepatic arterial supply (that need not be further discussed here). Ultimately the potentiality for regeneration, possessed by the liver cells and manifested to a remarkable degree, not only in the early but also in the late stages, gradually lessens and is finally lost, the general functional capacity of the liver cells being meanwhile compromised by the contracting connective tissue; the degenerative changes predominate over the regenerative and the patient soon dies, if he has not succumbed earlier to an accidental infection to which his depressed vitality renders him especially susceptible.

The conspicuous change in the cirrhotic liver at necropsy, then, is the evidences of regeneration of the liver parenchyma; the evidences of degeneration, though sufficiently manifest in early cases, in advanced cases are commonly past and represented only by the newly formed and rearranged liver tissue and the fibrosis; and the liver as a whole may be said to represent its, for a time at least, partially successful efforts to compensate the consequences of the continuous or intermittent activity of the etiologic factor—usually a poison, though in some cases possibly a substance causing thrombosis of the portal or hepatic artery radicles.

The idea of the primary change in cirrhosis being in the parenchymatous tissue is by no means new. It was entertained many years ago by Frerichs,[1] Ackermann,[2] Orth,[3] and others, and, indeed, Laënnec,[4] who originated the term, was not altogether wrong when he looked upon the "granules" as new-growth, though they can scarcely be considered neoplasms, as he believed; the likelihood or possibility of the primary changes being in the parenchymatous tissue is conceded by Ziegler,[5] Rolleston,[6] and others; its probability is suggested by the results of the work of the many observers who have studied the subject experimentally; it has recently been insisted upon by Kretz, Böstrom, and MacCallum; and it seems rather conclusively to have been proved recently by Pearce, who, experimenting with hemagglutinative serums, produced primary focal or widespread necrosis (depending upon the dose of the serum employed), with consecutive repair on the part of the liver cells and other changes that much resemble, though they are not identical with, cirrhosis as seen in man.

It behooves us, therefore, to discountenance, as far as possible, the use of the terms atrophic and hypertrophic, since a large liver may be atrophic to a noteworthy degree, and hypertrophy of the liver cells is a conspicuous feature of all small livers. Difficulties in the way of a satisfactory classification, however, are many, of which not the least important is the fact that different etiologic factors may cause similar changes in the liver (so-called atrophic cirrhosis with and without antecedent alcoholism), that one factor may give rise to different forms, so-called, of cirrhosis (thus, so-called atrophic cirrhosis, fatty cirrhosis, and hypertrophic cirrhosis may be preceded by definite alcoholism), and that many factors may be operative in the one case. Probably heretofore we have been too much concerned with the size of the liver, which nevertheless is a conspicuous clinical feature; but progress is more likely to be achieved by search for the etiologic factor than by too much attention to more or less disquieting clinical signs, and we have reason for believing that an organ like the liver, which possesses really remarkable inherent capabilities for repair, might, although considerably damaged, be able to establish functional sufficiency were the etiologic factor, whatever it may be, corrected or removed early—rather earlier, however, than the disease is usually recognized at the present time.

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[1] Klinik der Leberkrankheiten, 1861, vol. ii. p. 19 and Atlas. (Also translation by the New Sydenham Society.)

[2] Ueber hypertrophische und atrophische Lebercirrhose, Virchow's Archiv, 1880, vol lxxx p 306. Die Histogenese und Histologie der Lebercirrhose, Virchow's Archiv, 1889, vol. cxv. p. 216.

[3] Lehrbuch der spec. path. Anatomie, 1887, vol. i. p. 939.

[4] Traite de l'auscultation medicale, 1819, vol. i. p. 368.

[5] Lehrbuch der allg. Pathologie und path. Anatomie, 1898, 9te Aufl., vol. ii. p 591.

[6] Diseases of the Liver, Gall-bladder and Bile-ducts, 1905, p. 196.

Aneurism of the Descending Arch of the Aorta, Pointing in the Left Interscapular Space.

By M. H. FUSSELL, M.D.

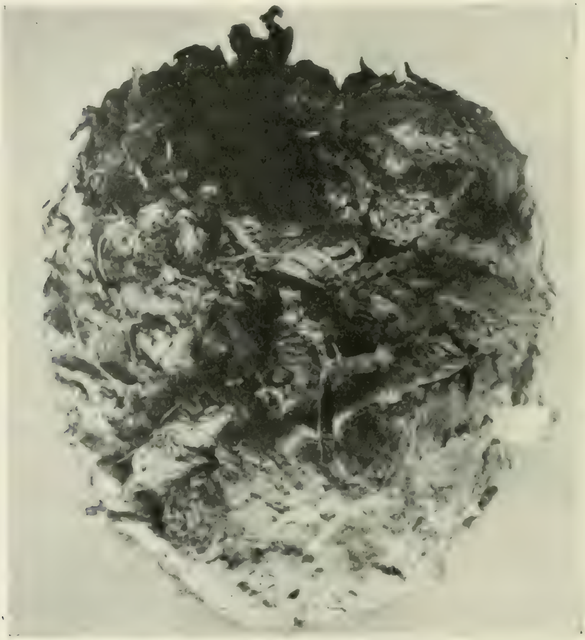
The patient from whom these specimens were removed was seen with Dr. Otto A. Rath, of the Falls of Schuylkill, at St. Timothy's Hospital, on October 25, 1904.

M. M., aged fifty years; married; no noteworthy family history. Had sore throat twenty years ago, with signs of secondary syphilis. Had miscarriage when young. Had pains in joints and bones when young. Began to complain two years ago with pain in left shoulder (paroxysmal). Noticed lump three weeks ago. Pain radiates to sides and in front. Difficulty in swallowing; cough for some weeks. Has rapidly lost flesh.

Physical Examination. Some distention of veins of both sides of neck, also in anterior portion of chest, especially on left. Marked pulsation of carotids. Marked prominence of junction of second rib and cartilage of right side; this swelling probably involves the joint. General fulness extending from parasternal line on right to inner third of clavicle on left, from sternal notch to third rib in median line. Over this fulness there is a visible pulsation. There is a marked inspiratory stridor. Apex beat of heart is seen and felt in midclavicular line in fifth interspace. No other abnormalities on front of chest. There is a circinate sore composed of small ulcerations the size of a split bean, the centre of mass being the seat of brownish pigmentation. Old scar of same character above elbow. None on right side. Posteriorly there is a marked prominence the size of half an orange, extending in the right interscapular space from just below line of the spine of scapula to one and one-half inches above lower angle of same. Over this is a marked expansile pulsation, no thrill, marked diastolic shock. Over fulness described in front there is systolic pulsation, followed by marked diastolic shock. Pupils equal. Left pulse less full than right. There is a marked tracheal tug.

Examination of Heart. The heart dulness cannot be developed accurately. The right border of heart is exactly over right edge of sternum. At the aortic cartilage a short, rather rough systolic murmur and a very markedly accentuated second sound. A systolic murmur of somewhat different type at the apex, and this can be heard in the axilla and over the pulmonary region. The pulmonary second sound not accentuated. Percussion of the upper portion of the chest shows an area of dulness corresponding to the area just described. Over this area is the same murmur that is heard over the body of the heart,

Fig. 1



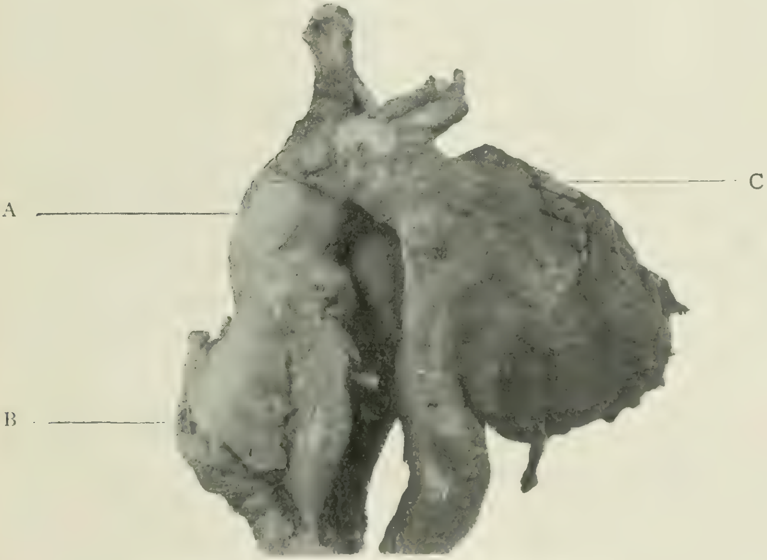
Clot containing wire.

and the murmur can be heard in the vessels of the neck also, but not so distinctly. Over the area of pulsation posteriorly the heart sounds can be heard, but not so marked. There is no murmur.

Examination of Lungs. Show no dulness posteriorly, but markedly prolonged expiration over left apex, high pitched in character. Over the trachea there is markedly harsh breathing, indicative of compression, and the same sound is observed over both apices.

On palpation, pain was constant under left shoulder blade. No expectoration, no headache, no pain in left arm. Some obstruction immediately back of sternum which necessitated several attempts at swallowing. Some dyspnea, no edema.

Fig. 2



A, dilated aorta. B, heart. C, aneurismal sac.

She was discharged from the hospital in three or four weeks unimproved. Three weeks after reaching her home the pain, dyspnea and pulsation in the mass became so annoying that it was determined to wire the sac. This was done by Dr. Hobart A. Hare. When the cannula was inserted blood did not spurt through the opening but dripped in drops, showing that the cannula was doubtless in an already formed clot; nevertheless, ten feet of gold wire was inserted, and an electric current passed through the wire for about one hour. No pain accompanied this procedure, nor was any distress felt afterward. There was no change in the tumor, either as regards resistance or pulsation. Immediately after the insertion of the wire an administration of morphine was necessary and she continued to take large doses of morphine until her death.

About one month after the wiring of the tumor I saw the patient again and found her with a large, left-sided, pleural effusion, with the ordinary physical signs. The liquid was removed. It returned on two occasions afterward and was removed each time. Emaciation of the patient continued, dyspnea became extreme, pulsation even more marked than previously, and she died of suffocation, March 4, 1905. At the autopsy the following notes were made:

The body is considerably emaciated. On the posterior aspect of the chest there is still a very large, soft mass about the size of a cocoanut. On separating the skin there is very little superficial fat found. No sign of any mass on the anterior portion of the chest. The right sternoclavicular joint is completely ossified so that the sternum and clavicle cannot be cut apart. The costal cartilages are much more calcified than is usual at the age of this individual. The pericardial sac contains an abnormal amount of fluid. Apex of heart found in the fifth interspace about midclavicular line. In the wall of the heart several sclerotic patches. The right ventricle contains soft, necrotic patch, probably postmortem. The right border of the heart is in about the midclavicular line and is formed by the right auricle. There is marked dilatation of the ascending portion of the arch of the aorta, the vessel extending in breadth from the left border of sternum to margin of the sternum and ribs on the right side. The left lung is adherent to the parietal pleuræ. One pint or more of liquid in left pleural cavity. The left lung is entirely collapsed. Upper lobe of the left lung is pressed down by a large mass filling the upper third of the left chest cavity.. This same mass extends to the right of spinal column. The descending portion of aorta admits three fingers when it is cut. The entire posterior wall of this mass is formed by lacerated ribs, body of vertebra, and skin. There is a most marked kyphosis which is due to ulceration and destruction of the bodies of the second and third vertebræ. The shafts of the second, third, fourth, and fifth ribs, for an area as large as an orange on left side, are completely ulcerated through.

The sac begins 1 inch from left subclavian, and descends upon descending portion of arch and descending thoracic aorta for 4 inches. The circumference is 13 inches in one direction and 12 inches in the other. The measurement of the aorta at the opening of the diaphragm is 1¼ inches. The circumference of the ascending arch of the aorta is 6¼ inches. The aortic opening is not greatly enlarged and apparently competent. Measurement from aortic valve to lower margin of sac 10½ inches. Transverse measurement of arch from outside of vessels, 5 inches. Circumference of the innominate artery, 2⅛ inches.

On examination of the blood clot it was found to be about the size of the two closed fists. In the center was found the wire which had been inserted during life. This was surrounded by a clot that was quite firm, though less dense than that on the edges. The wire had doubtless entered through the previously formed clot into the caliber of the sac, and had formed about this a new clot as stated above. The introduction of the wire, however, seemed to have no effect upon the progress of the disease.

DISCUSSION.

DR. STENGEL desired to call attention to the occurrence of pleural effusion in association with aneurism. That this is thought unusual was commented upon in the Section on Medicine of the College of Physicians, in which the subject was discussed. Dr. Stengel is, however, of the opinion that it is not so rare as some have believed.

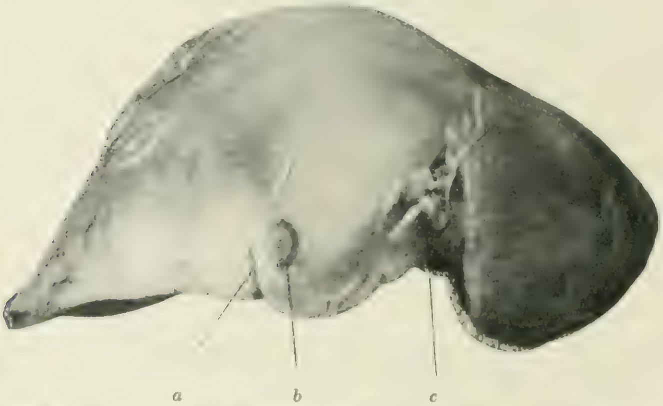
Intrahepatic Gall-bladder.

By HENRY S. WIEDER, M.D.

(From the Anatomic Department of the University of Pennsylvania.)

At the present time, when the surgery of the gall-bladder is occupying so much of the attention of surgeons in general, it may not be amiss to call attention to an anomaly of that organ which, when encountered during an operation, is likely to complicate matters to a very great if not insuperable degree; that is, "intrahepatic" gall-bladder. The specimen which called the attention of the writer to the condition and which he wishes to report was obtained from a case of his friend, Dr. Lowenburg, to whom he is indebted for the privilege of reporting it.

Fig. 1

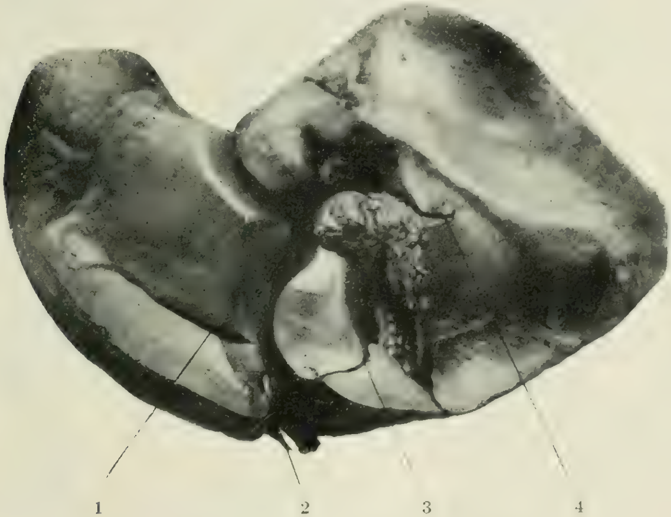


a, fissure for gall-bladder. *b*, gall-bladder. *c*, fissure for round ligament.

The patient was a child, aged fifteen days, the cause of whose death was not determinable, clinically, with a certainty, the child being apparently healthy until the day of death, when it suddenly became cyanosed and died shortly afterward. Autopsy showed nothing abnormal, excepting a patulous foramen ovale and this anomalous condition of the liver and gall-bladder, which has no clinical significance in this case.

The liver was found in its normal position, apparently not enlarged, measuring 10 x 6.5 x 3.5 cm., not adherent to any of the surrounding viscera, and almost completely enveloped by peritoneum, except for a very limited extent upon the posterior surface. The convex surface is smooth, of a dark-brown color, and shows the Liebermeister grooves produced by the ribs. The relative size of the right and the left lobes is about normal.

FIG. 2



Anomalous fissures upon under surface of the liver.

Situated 5 mm. above the free edge of the right lobe of the liver and 3 mm. to the left of the fissure which replaces the usual notch for the gall-bladder is seen a small, almost circular, slightly elevated, green cyst, which, upon being opened, allowed the escape of bile (Fig. 1). Examination of the lower surface of the liver shows the gall-bladder deeply embedded in the floor of the fissure bearing its name, but not covered by hepatic tissue. Five mm. from its termination the fissure deviates to the right and the gall-bladder leaves it, plunging into the hepatic tissue to appear on the convex surface, as previously described. In this manner the fundus of the gall-bladder becomes entirely surrounded by liver tissue, a bridge of hepatic tissue 5 mm. in thickness separating it from the free margin of the liver.

In addition to the above rare anomalous condition, there are also four anomalous fissures to be seen upon the under surface of this liver. One is a shallow fissure, 2.7 cm. in length, taking its origin from the fissure for the round ligament and running parallel to and 2 cm. from the free margin of the left lobe of the liver (No. 1, Fig. 2). Another very small and shallow fissure, 8 mm. long and branching at its centre to form a Y, is found on the left side of the fissure for the round ligament near its anterior termination (No. 2, Fig. 2). The third fissure, 12 mm. long and 5 mm. deep, taking its origin from the transverse fissure, is found in the right lobe running forward and to the right (No. 3, Fig. 2). The fourth and last fissure is found connecting the fissure for the gall-bladder with the fissure for the round ligament, thus bisecting the quadrate lobe. It is 2 to 5 mm. deep and runs 12 mm. from and almost parallel to the free margin of the quadrate lobe (No. 4, Fig. 2).

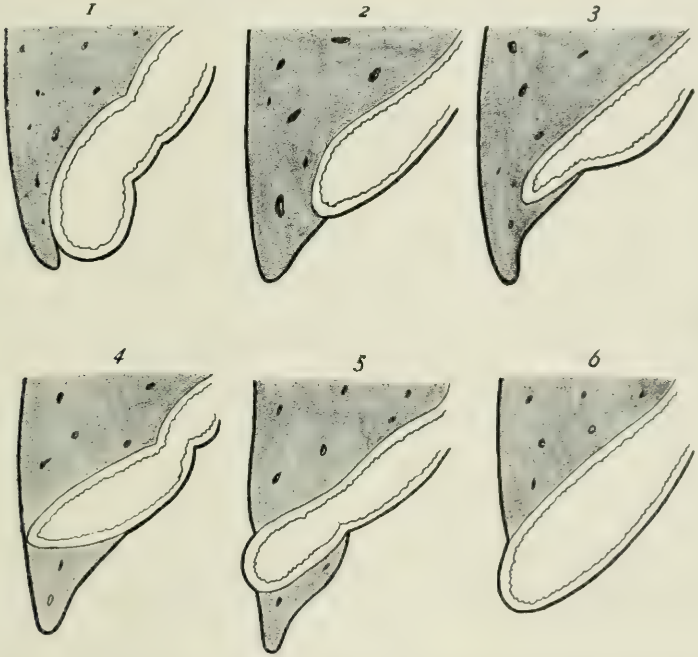
Before concluding the description of the liver attention is directed to the great depth of the fissure for the round ligament (Fig. 1), being 2 cm., while the bridge of hepatic tissue connecting the right and left lobes is only about 1.5 cm. in thickness. The umbilical vein is still patulous.

The writer has taken the liberty of calling the situation of this gall-bladder "intrahepatic," the name given it by Dévé,[1] in order that there may be some uniformity in the reports of this peculiar and interesting condition. A rather careful review of the literature, as far as the resources of the library of the College of Physicians would permit, fails to reveal any reference whatever to the condition here seen until 1903, when it was reported by Dévé before the Anatomical Society of Paris.

In a study of 130 infants, with the object of ascertaining the relative frequency of this condition, he encountered it in a dozen cases, and he marvels at the fact that it has never been recorded before. His paper reviews the matter very thoroughly, and we may, with considerable profit, review its most important points. He has divided the cases in which it occurs into the following three classes:

1. Those in which the tip of the fundus of the gall-bladder dips into the hepatic substance, but does not make itself evident upon the convex surface of the liver (No. 3, Fig. 3).

FIG. 3



1. Normal disposition of the gall-bladder as seen on cross-section. 2, 3, 4, and 5. Various types of intrahepatic gall-bladder. 6. Resultant condition seen in adult life.

2. Those in which the fundus of the gall-bladder buries itself in the hepatic tissue, but does not appear on the convex surface as a distinct cyst, but as an elevation covered by a very thin layer of liver tissue which is slightly bile-stained and thereby differentiated from the surrounding hepatic tissue (No. 4, Fig. 3).

3. Those in which the fundus of the gall-bladder pierces the liver tissue and appears on the convex surface as a cyst, as is shown in Fig. 1 and No. 5, Fig. 3. Fig. 3 illustrates Dévé's idea and is taken from his article.

In the majority of these cases the fundus of the gall-bladder alone is the portion of the organ involved, so that there may be some objection to the name intrahepatic gall-bladder. Dévé defends the title on the ground that the extent of gall-bladder enveloped varies, he having seen at least one case in which the gall-bladder was buried in the liver tissue for two-thirds of its extent. He makes the positive statement that this condition is found only in infants, and explains this by atrophy of the bridge of hepatic tissue, owing to the mechanic action of the distending gall-bladder pressing up against the anterior abdominal wall. He substantiates this statement with observations upon adult livers in which he found the gall-bladder in a deep groove, and at the level of the fundus he found vestiges of hepatic tissue with vessels disappearing in the neighboring parenchyma.

The above statement the writer believes is true in the great majority of cases, having seen a specimen in the Pathologic Laboratory of the University of Pennsylvania, showing the gall-bladder deeply grooving the fissure for the gall-bladder with obliteration of the usual hepato-vesicular *cul-de-sac* at the fundus of the organ. The pathologic records of the University of Pennsylvania also contain the record of one of Dr. Riesman's cases, autopsy performed by Dr. Smith, in which the gall bladder was found in a very deep notch on the anterior aspect of the liver, the notch being so deep that the lowermost portions of the gall-bladder were not below the edge of the liver. As further evidence that this was probably in infancy an intrahepatic gall-bladder, the liver tissue directly above the gall-bladder was very thin and parchment-like and more of grayish hue than the remainder of the liver.

While, as the writer has stated before, and has endeavored to prove by the cases cited, he believes that this condition does not occur very frequently in the adult, nevertheless, the statement of Dévé that it never occurs except in infancy is wrong, as is shown by the cases recently reported by O'Day[2] and Lemon.[5] O'Day's case, similar anatomically to the one shown in Fig. 1, occurred in an adult and was found on the operating table during an operation for gallstones.

Lemon's case was much more remarkable. It was encountered during an operation for gallstones by Dr. W. K. Bouton, of Melbourne. To quote Lemon's description, "after opening the abdomen (the liver presenting itself in the operation wound), what appeared to be an hydatid cyst was seen on the anterior surface of the right lobe—a slightly rounded elevation of pale yellowish color. On lifting the liver forward a similar though somewhat more projecting eminence appeared on the posterior (inferior) surface which, when viewed through the substance of the liver, was quite translucent. It was in the normal position for a gall-bladder, but the surfaces, both anterior and posterior, were continuous with liver substance. As no gall-bladder could be discovered an incision was made on the posterior (inferior) surface into the swelling, when bile gushed out, and on further exploration two large gallstones, one barrel-shaped and the other conical, were secured; there was an additional facet on the barrel-shaped stone, showing that a third stone had been present, but as a probe passed the whole length of the common duct without striking one, it had evidently been passed previously. The edge of the incision into the gall-bladder at the time of operation was at least three-eighths of an inch thick, the circularly arranged coat of the gall-bladder being marked off very definitely from the liver substance on the one hand and from the mucosa, etc., of the bladder on the other." This is, without doubt, the most marked, and, in fact, the only true case of intrahepatic gall-bladder ever reported, and nevertheless it was found in an adult.

In addition to refuting the statement of Dévé, those two cases, since they both contained gallstones, demonstrate two very important facts—viz., that when the condition persists into adult life it is most liable to be the seat of gallstones, and that the contractile power of the normally free gall-bladder probably has much to do with the prevention of the formation of gallstones. It is the opinion of the writer that the gallstones were present in these cases and will probably be present in all cases of intrahepatic gall-bladder in adult life.

because of the fact that the organ has rigid walls and is therefore unable to expell any excess of mucus, inspissated bile, etc., that may be present as a result of hyperemia or some slight catarrhal condition of the mucous membrane. This mucus or inspissated bile forms a favorable site for the growth of bacteria that may gain access to the gall-bladder or favorable nidus for the further deposit of cholesterin and bile salts, and thus we have the formation of stones. Again, having no contractile power, the gall-bladder is unable to expell stones when formed, so that they probably give no symptoms until the organ becomes overfull or one, by gravity, becomes engaged in the cystic or common duct. Occurring in adults, as we have seen, this condition becomes important from the etiologic standpoint in its relation to gallstones and from the operative standpoint. It is very easy to realize how such a condition or even the more superficial disposition of the organ described by Dévé as occurring in adults may seriously hamper the surgeon in operating upon it.

Dévé makes the statement that in these cases of intrahepatic gall-bladder the fissure for that organ is never seen on the anterior aspect of the liver, but that its place is taken by an elevation of the free margin of the liver. This also, the writer thinks, may be true in the great majority of cases, but that it is not always the case is shown by the specimen shown in Fig. 1, for in it that fissure can be seen as a distinct incisure of the free margin about 5 mm. long.

The cases of Dévé, O'Day, and Lemon are the only recorded cases the writer has been able to find, but as the result of inquiry, he has found that Dr. Hand, of this city, encountered a case a few years ago in a child about seven years of age. This case has not been reported, but was similar in the relations of the gall-bladder to the one reported in this article.

The only fact that now remains to be considered is the cause of this peculiar disposition of the gall-bladder. A cursory examination is sufficient to convince one that it is not a pathologic condition, but that it is rather some congenital misplacement, the cause of which is rather hard to explain. When we consider that the gall-bladder is an outgrowth from the bile-duct beginning about the second month,[3] and that the bile duct itself is an outgrowth from the duodenum separate from and independent of the liver, and if we accept the conclusion of Thompson, who says: "The gall-bladder appears to develop along the bottom of a fissure (in the liver), which extends forward to the anterior border and which apparently is formed prior to the appearance of the vesicle," the most plausible explanation that suggests itself is that offered by Dévé. He believes it is the result of the general tendency of the human liver toward the obliteration of the various interlobular fissures which are so marked in the majority of mammals. Thus we get a union of the quadrate lobe with the right lobe in the same manner as the two primitive lobules of the left lobe are united to form one, and in the process of this union, which takes place after the full growth of the gall-bladder, the fundus of that organ is surrounded by liver tissue. Until a better explanation is forthcoming, the one of Dévé will probably have to stand, in spite of the fact that in this case there has been no obliteration of the fissure for the gall-bladder and there is a tendency for the fissure not to close, as evidenced by the four anomalous fissures and the great depth of the fissure for the round ligament.

References.

1. De quelques particularities anatomiques et anomalies de la vesicule biliaire, par le Dr. F. Dévé, Bulletins et Mémoires de la Société Anatomique de Paris, 1903, S. 6, tome v. pp. 261 and 266.

2. Gall-bladder through Foramen in Liver, by J. C. O'Day, Oil City, Pa. Journal of the American Medical Association, April 22, 1905, No. 16, vol. xliv, p. 1281.

3. Diseases of the Liver and Gall-bladder, by H. J. Waring.

4. Fissures of the Gall-bladder, by J. Thompson, Journ. Anat. and Phys., vol. xxxiii. pp. 47 and 64.

5. Anatomic Peculiarities of a Gall-bladder and an Appendix, F. Lemon, Hawthorne, Australia, Lancet, London, May 13, 1905.

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A Study of the Elastic Tissues in the Parous and the Non-parous Uterus.

BY BROOKE M. ANSPACH, M.D.

IN order to make a description of the elastica plain, it will be necessary to state that according to Kreitzer there are four layers of muscle in the uterine wall. There is first the layer containing the large bloodvessels, spoken of as the stratum vasculare, which occupies the largest part of the myometrium; running between this and the mucosa is a layer whose general direction is longitudinal, spoken of as the stratum submucosum. An outer layer, running longitudinally directly under the serous coat is given the name stratum subserosum. The irregular fibers between the later stratum and the vascular layer are known as the stratum supravasculare.

The elastic tissue of the uterus is derived from two main sources. First, the serous coat; second, the bloodvessels. In the subserous and in the supravascular layers the elastic fibers are very rich. They surround the individual muscle cells in the outer layer, forming elastic perimysia. They are not subdivided to this extent in the supravascular layer. Their general direction is toward the endometrium and as the outer muscular layer is longitudinal and the supravascular layer is more or less circular, they run at right angles to these muscle bundles. In the vascular layer the elastica is mostly confined to the vascular channels. In the submucosa there is practically no elastica except in the vessels. The elastic tissue of the subserous and supravascular layers appears as fine, unbroken fibers of a more or less uniform thickness. Many of them are quite straight, especially those taking a centripetal course. In the vascular layer elastic tissue is found surrounding the lymph spaces, the capillaries, the veins, and the arteries. About lymph spaces they appear as short, wavy fibers or as black points; their distribution is quite irregular and the number is always small. This is true also of the capillaries. In the veins there is a collection of elastic tissue between the inner and the outer coat. It is quite irregular and forms no distinct limiting band, as in the arteries. In the small and medium sized arteries there is a distinct limiting membrane of elastic tissue between the intima and the media, the internal elastic membrane; and between the media and the adventitia in the larger vessels is another, the external elastic membrane.

Pick draws attention to the arrangement of elastic tissue in the uterus as being highly significant. The preponderance of the fibrils in the subserous and the supravascular layers, their definite direction (centripetal) toward the endometrial cavity, their fine subdivision so that in the outer layer they surround each individual muscle cell, all of this he believes shows they have a very well-defined purpose. They serve not only for the support of the blood and lymph capillaries and the nerves, but further than this they reinforce the muscular action of the uterus, protect it from being overstretched, and make easier its return to a passive state after either distention or contraction.

The study I have made is based on twenty-three specimens. Five of these were uteri from women who had uncontrollable metrorrhagia to which none of the usual causes could be ascribed. The other eighteen were specimens removed along with the appendages in pelvic inflammatory disease. The uterus in such cases is not much affected.

The subjects from which these uteri were taken varied in age from seventeen to fifty-six. Five of the women were nulliparous, thirteen were parous. The five uteri from the metrorrhagia cases were all multiparous.

Sections were taken from the same part of the uterus in each case; they were cut of the same thickness and they were stained for the same length of time by Weigert's resorcin fuchsin method.

There are very striking changes in the elastic tissue as the result of pregnancy, and the greater the number of pregnancies the greater are these changes. It is quite easy to say from a section of the muscle of the uterus stained by the resorcin fuchsin stain whether the woman has had children or not. The alterations of the elastica affect not only that in the two outer layers of the myometrium, but also that in the vascular channels. The elastic tissue in the subserous and in the supravascular coat becomes increased in amount and the fibers are shorter, thicker, show a tendency to become clumped together, and are curly rather than straight.

In the vessels wherever elastic tissue is present normally the amount is very much increased; the fibers showing the same tendency to become broken, thick and gathered into clumps. The vessel changes, which were observed in these cases may be spoken of as intramural and perivascular. The intramural changes in the arteries consist of a broadening and splitting of the internal elastic membrane. It no longer consists of a fine single line, but is irregular and three or four times its normal thickness. The elastica of the veins in this form (intramural) is similarly increased.

Another form of elastic hypertrophy, the perivascular, occurs in the adventitia. The entire adventitia is represented by heavy masses of elastic tissue in which no small fibrils are seen—the tissue appears a dense black. In sections stained by Van Gieson's stain these same areas appear bright yellow, and with hematoxylin and eosin they are granular, pink and contain scattered well-preserved nuclei. The internal elastic membrane in such cases may be fairly normal. This degeneration, perivascular, increases in some cases until it occupies the entire wall of the artery. Such a vessel is bright yellow by Van Gieson's stain and of a granular pink color by eosin hematoxylin, while densely black with Weigert's stain.

The same dense deposit of elastic tissue occurs in the outer coat of the larger veins.

These areas here appear bright yellow by Van Gieson's stain and pinkish yellow by hematoxylin eosin.

From this study it appears that the above alterations in the elastic tissue are the result of pregnancy. They are not the result of age, for in two nullipara aged thirty-seven, they did not occur and in a primipara aged forty-one they were not marked.

These changes in the uterine vessels which are often spoken of as arteriosclerosis are the result of pregnancy and must be considered normal. They are much more constant and notable than the increase in the relative proportion of fibrous tissue which often follows pregnancy. *December* 14, 1905.

Congenital Malformations of the Heart; A Series of Cases.

By ALLER G. ELLIS, B.Sc., M.D.

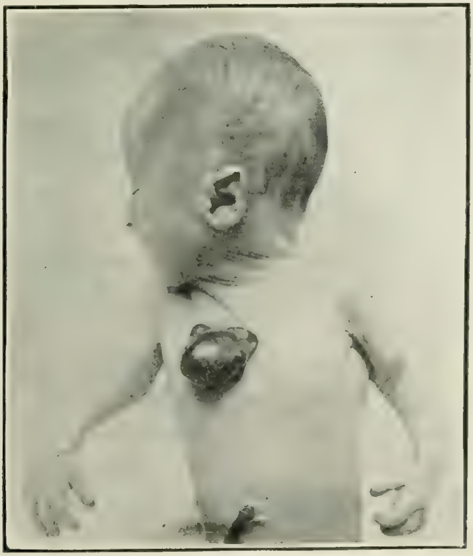
(From the Laboratories of the Jefferson Medical College and the Philadelphia General Hospital.)

CONGENITAL malformations of the heart, both singly and in their varied combinations, form a group of cases of perennial interest alike to the clinician and to the pathologist. The characters making up the symptom-complex during life, although not constant and hence rarely leading to accurate diagnosis of the exact lesion, are nevertheless quite well known; the possibilities of autopsy findings are bewildering. A study of over 600 reported cases, which by no means exhausts the enormous literature on the subject reveals forty-five different single or combined lesions of the heart and great vessels. This fact renders impracticable my original intention to classify the cases according to the nature of the malformation, and I shall speak in particular only of those lesions, seven in number, which are represented by the specimens on exhibition. It is interesting to note, however, that the forty-five cases of cardiac malformation found among the 3875 autopsies, with complete records, performed at the Philadelphia Hospital during the past thirteen years are grouped as follows:

Patent foramen ovale	31
Patent ductus arteriosus	1
Absence of auricular septum	1
Absence of anterior portion of auricular septum	1
Patent foramen ovale and patent ductus arteriosus	10
Patent foramen ovale, patent ductus, pulmonary stenosis and perforate interventricular septum	1
Patent foramen ovale, patent ductus, and transposition of aorta and pulmonary artery	1

In the sixty autopsies I have held elsewhere than at the Philadelphia Hospital I have found five instances of patent foramen ovale.

Case I.—*Ectopia Cordis.* This specimen was recently acquired by the museum of the Jefferson Medical College through the courtesy of Dr. George Cunningham. The child is a full-term male.



Case I.

The lateral halves of the sternum are united except for a distance of 2 cm. at the lower extremity, the gap between the parts being 5 cm. wide. The heart is entirely external to the thoracic wall, the vessels passing in through an oblong and diagonally placed opening 2 by 3.5 cm. in size. The organ is covered by visceral pericardium only and can be drawn some distance from the chest by exerting traction upon the great vessels. The latter structures, as well as the heart, are entirely free from the margin of the opening in the skin and underlying tissues. The auricles are rounded and project prominently; the apex is blunt and is formed nearly equally by the two ventricles. The heart is essentially normal in size. As observed by the nurse, the organ performed its functions properly while the child lived, a period of twenty-three and one-half hours.

Ectopia of the heart may be associated with fissure of the sternum, exocardia or pectoral heart, as in the present instance, or with an intact sternum the organ may be situated in the neck (cervical heart) or in the abdomen (abdominal heart). Instances of the first-named group are the most common and include those with entire separation of the sternum and those with superior and inferior defect, respectively. The condition is relatively rarely found alone, being usually accompanied by protrusion of the abdominal viscera. Peacock[1] cites thirteen cases of the various types reported by others and describes another specimen in the Museum of St. Thomas' Hospital. Ballantyne[2] mentions nine additional cases, and states that others have been reported. He refers to nine cases of the sternoepigastric type collected by Taruffi,[3] but as the entire sternum and the abdominal wall to the umbilicus were divided, Ballantyne regards these cases as more properly belonging under gastroschisis. I have obtained references to three cases not included in the series mentioned.

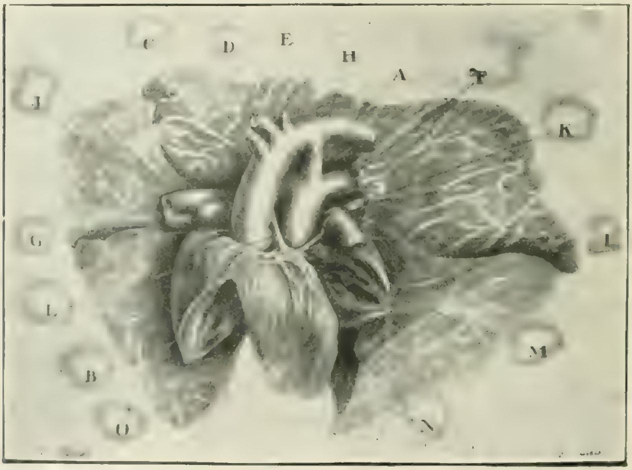
When the halves of the sternum are entirely separated, the pericardium is usually absent; the heart itself may be normal or exhibit varied malformations. In a case of this type reported by Grant[4] the subject was a seven months' fetus, which lived six hours in an incubator. The halves of the sternum were 5 cm. apart at the upper and 10 cm. at the lower end, and the extreme upper portions of the recti muscles were slightly separated. The visceral pericardium was reflected from the heart and joined to the skin. At each systole the heart was tilted upward, the apex reaching the chin.

An example of superior defect of the sternum is the case of Sidney Jones, cited by Peacock. It differed from my case in that the skin was prolonged over the great vessels and thence to the base of the heart, the epithelium extending a short distance on the auricular walls. The child was born at the eighth month and lived thirteen hours. When the opening involves the lower part of the sternum and the epigastric region the pericardium is not unusually present and the person may reach adult life. In the case reported by Goode[5] the manubrium was intact, the heart protruding below through the passage of the bloodvessels, with the covering of which the skin at the lower border of the foramen was continuous. The heart was normal in size and shape; it was kept bathed with olive oil and covered by a pasteboard cone. The child lived sixteen days. In the absence of defect in the sternum an opening in the diaphragm may allow of the condition of abdominal heart, with or without external tumor. In the case reported by Holt,[6] a living child five months of age, with umbilical hernia, the heart was situated below the ensiform cartilage, the circulation beng fairly well maintained. Peacock cites the case of Deschamps who, at autopsy upon the body of a soldier, found the heart occupying the usual position of the right kidney, the vessels passing into the thorax through an opening in the diaphragm.

Ballantyne states that ectopia cordis is rare in human beings and presents several difficult problems in teratogenesis; the theory of arrested development is permissible. Non-separation of the membranes may prevent fusion of the body walls in the middle line and amniotic adhesions may hold the heart forward. In cases in which the heart is covered by skin, the pressure and adhesions may have ceased early enough to allow the walls to close imperfectly. As the presence of the heart external to the body is incompatible with the maintenance of life, an interesting question is raised by the case of Lannelongue. In that instance a thin membrane which covered the heart sloughed on the fifteenth day; the skin margins were then united over the heart and the patient recovered. It appears reasonable that when the conditions are even in the least degree favorable to surgical interference, such a step should be carefully considered as a possible means of saving life.

CASE II.—*Transposition of the Aorta and Pulmonary Artery; Patent Foramen Ovale; Patent Ductus Arteriosus.* This case has elsewhere[7] been reported at length and will here be only briefly described.

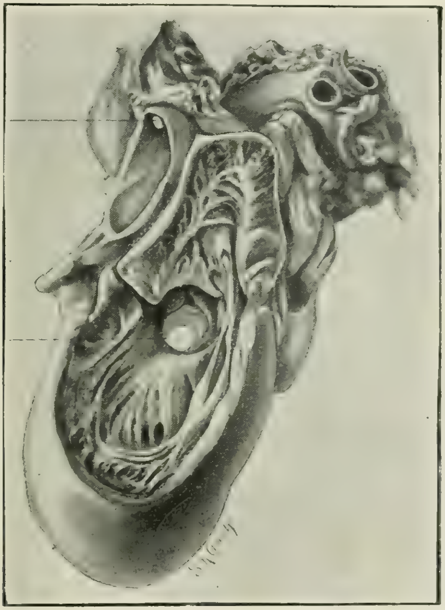
The subject was a male infant who died at the age of thirty-four days. At birth it weighed seven pounds and the day before death seven and one-quarter pounds. Respiratory difficulty was at all times present and cyanosis was marked during the first few days. Later the blueness became less prominent, especially at short periods, during which it almost disappeared. The child died during an attack of labored and irregular breathing accompanied by extreme cyanosis. The pathologic diagnosis was: transposition of the aorta and pulmonary artery; patent foramen ovale; patent ductus arteriosus; hypertrophy of right ventricle; partial atelectasis of left lung; general visceral congestion. The heart is essentially normal in size. In thickness the wall of the right ventricle is 7 mm., of the left, 5 mm. Neither the aorta nor pulmonary artery shows evidence of stenosis. The foramen ovale is patulous in the shape of a slit-like opening 0.5 cm. long. The ductus arteriosus allows with ease the passage of a probe 2 mm. in diameter.



Case II.

Cases of transposition of the great vessels of the heart are not extremely rare, probably as many as seventy-five being recorded. The malformation in origin is developmental rather than fetal in point of time, being due to lack of rotation of the septum in the aortic bulb. It is incompatible with long life, practically all of the subjects dying before the age of three years. A coexistent opening in the interventricular septum favors the prolongation of life. There are no pathognomonic physical signs or symptoms of transposition and the clinical diagnosis can be made only by inference; even this is rarely done.

CASE III.—*Patent Interventricular Septum; Pulmonary Stenosis; Patulous Foramen Ovale; Patulous Ductus Arteriosus.* This specimen was obtained at an autopsy held by Dr. Coplin at the Philadelphia Hospital upon a male child of eleven months, the diagnosis of the three first-named lesions having been made during life by the attending physician, Dr. McKee. The body was extremely emaciated and the gums were spongy. The cavities of the right side of the heart, which is a globular organ, were found distended with blood. The right auricle communicates with the left through an oblique slit in the foramen ovale 3 mm. in maximum size. The pulmonary



Case III.

artery arises from the right ventricle at about its normal position, the conus pulmonalis being narrowed. At its point of origin the artery is 7 mm., and 1 cm. beyond this, 2 cm. in circumference and the orifice is guarded by a single, very thick, crescentic leaflet. From the artery 2 cm. beyond its origin springs the ductus arteriosus, which enters the aorta 2.5 cm. from its valves. The right ventricle at the base communicates with the left through a somewhat triangular opening in the membranous septum, the apex being directed toward the apex of the heart, and each side measuring 4 mm. in length. As a result of this septal defect both ventricles open into the aorta immediately over the septum. The wall of the right ventricle is 7 mm., of the left, 5 mm. in thickness.

Of this combination of lesions perforate interventricular septum is not infrequent, though not at all uncommon. The opening is usually anterior or posterior, most often the former, to the pars membranacea, or undefended space. Hart[8] states that perforation of the membranous septum can occur only as the result of inflammation and is very rare. The fact that deficiency is usually in the posterior part of the anterior segment of the septum is of interest in connection with the question of heart block as related to the auriculoventricular muscle bundle of His. The latter structure passes down along the upper edge of the muscular septum where that tissue joins with the membranous portion and terminates below the root of the aorta. The possibility of interference with this band when the defect is in the posterior segment of the septum appears worthy of note, although I know of no recorded case of heart block associated with such malformation. The presence of deficiency in any one of the three parts of the septum is not incompatible with the attainment of adult life. Cyanosis may or may not be a symptom of the lesion. Reiss has called attention to the fact that cyanosis may be absent in early life and later make its appearance.

Communication between the ventricles is due to maldevelopment of one of the several component parts of the septum and not uncommonly occurs in connection with stenosis or atresia of the pulmonary artery. Keith[9] furnishes an admirable discussion of this question in connection with a series of 30 malformed hearts, which he exhibited. Of the 185 specimens of malformation of the heart in the London museums, all of which he has studied, 113 show developmental error in the conus pulmonalis and 22 additional organs congenital stenosis of the pulmonary valves alone. In a large number of the 113 specimens there is an interventricular opening. Keith directs attention to three features in the septal wall of the infundibular portion of the right ventricle which are at present little noticed by anatomists. They consist of a furrow and two muscle bands and their evolution, together with the expansion of the conus pulmonalis, has much to do with the closure of the interventricular foramen. The persistence of the foramen is usually accompanied by patulous foramen ovale. Antemortem diagnosis of ventricular communication is possible, as mentioned in the present instance. Most prominent is a murmur which is loud, systolic or almost continuous in time, and may be heard over the larger part of the chest; it is loudest along the course of the interventricular septum.

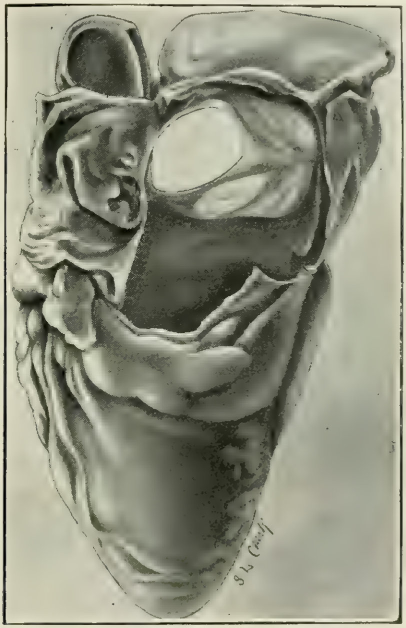
Pulmonary stenosis is considered by the great majority of writers to be the most common of congenital malformations of the heart; this is well attested by the statistics of Keith and by Peacock's 119 cases among 181 of congenital anomaly. Complete atresia of the artery is less common than is stenosis. Stifel states that of the cases of atresia the artery is only a string-like cord in 13 per cent., the ductus arteriosus is open in 82 per cent., the foramen ovale in 61 per cent., and there is a defect in the interventricular septum in 76 per cent. In simple stenosis the ductus is seldom, the foramen ovale frequently, open. In one of McCrae's[10] cases of atresia with deficient auricular septum and open ductus a fetal systolic murmur was demonstrated to students before the birth of the child. In this subject there was also transposition of the viscera, a condition of which Arneill in 1902 collated more than 300 cases. In some of these instances the malposed heart is also malformed, but the former condition does not appear specially to predispose to malformation. A moot point regarding pulmonary stenosis is its influence upon the incidence of tuberculosis of the lungs. The common belief is that this malformation does favor the disease in question. Burke[11] regards this occurrence of pulmonary tuberculosis, which was present in all three of his cases, as due not to pulmonary stenosis but to coexisting narrowing of the aorta.

Persistence of the ductus arteriosus is a postnatal malformation. It is exceedingly rare as a single lesion, being almost always associated with one or more other cardiac or vascular defects. Clinically, an interesting point is the possibility of diagnosis. An elaborate symptom-complex of the lesion is given by various writers, but the most prominent feature regarding them is the regularity with which they fail. Arnheim[12] reports a case in which what seemed a clear diagnosis of open ductus was not confirmed by autopsy, and Burke (*loc. cit.*) cites three such cases. The latter concludes with the assertion that the accentuation of the pulmonary second sound in pulmonary stenosis as a proof of the existence of open ductus, though possible, is supported by absolutely no facts. He believes that such accentuation is an auricular tone and is diagnostic of open foramen ovale, which was present in all three instances.

Case IV.—*Absence of Anterior Portion of Auricular Septum.* This specimen is also from a Philadelphia Hospital case, being obtained by Dr. Coplin from a woman of thirty-two, who died of carcinoma of the uterus. There had been no clinical evidence of cardiac anomaly. The opening occupies the anterior portion of the auricular septum and is 32 mm. in diameter. Cases of partial absence of the septum are not uncommon, of the entire septum rare; instances of non-closure of the foramen ovale are exceedingly numerous. These openings, even when of large size, are usually of little or no clinical importance, appearing to exert no direct effect upon the circulation. When a large auricular opening is present in cases of mitral stenosis, blood may pass to the right auricle and give rise to jugular venous pulse in the neck. The possibility of paradoxic or crossed embolism must always be borne in mind in connection with such lesion.

In order to determine if the myocardium of malformed hearts showed histologic differences from that of normal organs, sections were made from the left ventricle in Case II. and from both left and right ventricles in Cases III. and IV. Microscopic study shows no noteworthy changes as compared with the usual histologic appearance of the normal myocardium nor is there appreciable difference between the two sides of the heart in the last two cases. The specimens, however, had been in preserving fluids for at least several months before this study was made and the findings cannot be regarded as conclusive.

The influence of heredity in the production of malformation of the heart appears to be positive. In my previous paper I cited several series which point to the active role of this factor. Of interest in this connection, though not exactly similar, is the case reported by Boinet.[13] A woman of twenty-three, who for three years had mitral stenosis, which followed pneumonia, died as the effect of a second attack of pneumonia and aborting a six months' fetus. Autopsy on mother and fetus showed similar lesions of the mitral valve in each, the process not being so advanced in the latter, although distinct fibrous nodules were present on the leaflets. The fetus was normal in every other respect and syphilis and tuberculosis could be eliminated as causes. Boinet considers it probable that the first attack of pneumonia caused endocarditis in the mother and later this lesion was transmitted to the fetus.



Case IV.

It is a pleasure to acknowledge the aid in searching the literature of this subject rendered by Max Meitzner and H. L. Hull, research students in the Jefferson Medical College.

References.

1. Malformations of the Heart, 1866.
2. Manual of Antenatal Pathology and Hygiene: The Embryo, 1904.
3. Storia della Teratologia, 1894, viii. 410.
4. Brit. Med. Journal, 1896, ii. p. 1639.
5. Virginia Semi-Monthly Med. Journal, 1903–04, viii., 555.
6. Medical News, No. 24, vol. lxxi. p. 769.
7. American Journal of Obstetrics, December, 1905.
8. Virchow's Archiv, Band clxxxi, Heft 1.
9. Proc. Anatom. Soc. of Great Britain and Ireland, 1904–05.
10. Journal of Anatomy and Physiology, October, 1905.
11. Buffalo Med. Journal, August and September, 1902.
12. Berl. klin. Wochenschrift, February 20, 1905.
13. Bull. Acad. de Med. de Paris, February, 1905, No. 8.

December 28, 1905.

Case of Cystic Left Kidney and Calculus of the Right Kidney.

By M. H. FUSSELL, M.D.

The patient from whom these specimens were removed was admitted to St. Timothy's Hospital August 21, 1905, with symptoms of stone in the kidney.

An *x*-ray picture showed three shadows toward the lower pole of the right kidney. No definite history was obtained except that of stone. After he had been in the hospital three days, however, he complained rather suddenly of distention of the abdomen, and we were told by his mother that he had a lump in his abdomen since his childhood; the lump was sometimes large, sometimes small, and sometimes disappeared.

On examination of the abdomen on August 25, 1905, a large mass was seen occupying the lower three-fourths of the abdominal cavity. This mass was cystic and not very painful. On the 28th, the mass had markedly increased in size, the dulness extending upward, posteriorly to the fifth rib, and laterally to the seventh rib, the mass was still painless, and there was marked fluctuation. On the 30th the mass extended toward the right until the right edge was midway between the umbilicus and the right side of the abdomen.

At this time the patient gave evidence of so much distress that the tumor was tapped by Dr. Wood. Soon the patient died of uremia.

An autopsy was not allowed, but both kidneys were removed through the original opening; the left was found to be a huge cystic kidney, measuring from the upper to the lower extent of the pelvis around the poles of the kidney 56 cm., the length of the kidney was 33 cm., the length of the pelvis was 20 cm., the transverse circumference with the pelvis distended was 41 cm., the longitude and circumference 72 cm.

Though the specimen was removed through a small opening the ureter was carefully examined to the bladder and no obstruction was found. The kidney consisted of a great number of cysts varying in size from that of a walnut to that of a man's fist.

Through the surface are small areas which resemble normal tissue, the capsule is greatly thickened, but somewhat easily detached. The pelvis is greatly distended, the ureter is not at all dilated, is patulous and comes off the lower part of the pelvis and is placed at the proper angle. On section of the right kidney it seems to be rather larger than normal but healthy. In the distinctly distended calices are found *eight* stones: two in the pole, both being embedded in the kidney substance, three about in the middle of the kidney, and four in the lower pole.

It seems probable from the appearance of this cyst that it is not a congenitally cystic kidney; the cysts are too large, and there is no obstruction of the ureter of congenital origin. On the other hand there is no evidence of stone, the commonest cause of postnatal hydronephrosis. It would appear from the fact that the ureter is not dilated and that there was no stone in the pelvis that obstructions might easily have occurred by a kinking of the ureter close to the pelvis of a movable kidney. It is certain from our own observation that the tumor varied in size. When the patient entered the hospital no tumor was observed, though there is no record of a careful abdominal examination. As he passed through the hands of several physicians and nurses, and had an *x*-ray taken before the tumor was observed, the mass was certainly not very large and could not have been the size it had attained when seen by the writer. These facts, together with the history of a tumor which had appeared and disappeared through a long series of years, make this case certainly one of intermittent hydronephrosis, due to intermittent constriction of the ureter close to the pelvis. As is well known, cysts of the kidney are either congenital or acquired. The congenital cystic kidneys are usually bilateral, have as their cause either a formation of many small cysts, or an obstruction of the pelvis or ureter by membranous divisions.

The commonest cause for acquired hydronephrosis is a stone, though a kinking of the ureter or pressure from a tumor may be the cause. Where the obstruction is in the ureter the ureter is dilated between the point of obstruction and the pelvis.

Another point of interest in the case is the multiple renal calculi in the right kidney. Eight stones is certainly a very unusual number, and the stones were faceted and had the appearance of biliary calculi.

No analysis of these stones has been made; however, the light-brown color and the faceted appearance, according to Ziegler, would mark them as probably composed of phosphate of calcium.

October 26, 1905.

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The Spirochetæ Found in Syphilis.

BY RANDLE C. ROSENBERGER, M.D.

(From the Clinical Laboratory of the Philadelphia Hospital.)

ANY discovery which seems to bring us nearer to the specific cause of a disease is hailed with great enthusiasm. Usually such discoveries are based upon the study of but few cases, and, in the majority, the results are not supported by extended observations. Recently it has been maintained that the cause of syphilis has been discovered, and it appears, from the number of successful results obtained by others than the original discoverers, that something definite has been achieved.

Schaudinn and Hoffmann (*Arbeiten aus dem Kaiserlichen Gesundheitsamte*, Berlin, April 10, Heft ii. p. 527) call attention to a very delicate organism which they found constantly in syphilitic lesions, and which they term the Spirocheta pallida. Occurring with this parasite was another, larger, darker organism, the Spirocheta refringens. They found these parasites in the juice of glands, chancres, and flat condylomata. Material from these sources was examined fresh and in stained preparations. The Spirocheta pallida is described as being extremely difficult to see in the fresh state, and very refractory to stains. It varies in length from four to fourteen microns, the width from an immeasurable thickness to five-tenths of a micron, and the number of bends or curves from three to twelve. It is motile, showing a rotary motion, forward and backward, and a bending of the entire body. There is said to be a suggestion of an undulating membrane, but no flagella; the ends are pointed quite sharply. The Spirocheta refringens was found in non-syphilitic lesions, while the Spirocheta pallida was not.

Three years previously Bordet and Gengou had observed the same organism in the initial lesions of syphilis, but not finding them constantly they discontinued their observations.

The first studies of Schaudinn and Hoffmann embraced twenty-six cases of syphilis. In every case they found the specific organism. Schaudinn in a later communication (*Berl. klin. Woch.*, May 29, 1905), found the parasite in the deeper layers of primary lesions, inguinal glands and in the splenic blood obtained one day before the appearance of roseola. He says that in general morphology it is a thin, spirally twisted thread; and there is seen an undulatory movement which passes along the whole structure, expressive of an undulatory membrane. With this are associated bending, snake-like and whip-like movements of the whole body; spirillæ differ from this in that they have a rigid long axis. The organism also differs from the spirillæ in its minute size, its delicacy and its refractility. The spiral turns are numerous, regular and deep, and they hold this morphology in stained preparations. Schaudinn was able to demonstrate the parasite in twelve cases of typically syphilitic glands (inguinal); it was often found only after a very diligent search. He was not able to find the Spirocheta pallida in bubo following soft chancre, or in carcinomatous or tuberculous tissue. In a male who exhibited no syphilitic phenomena for nine years he found large spirochetæ in an erosion of the glans penis.

Hoffmann (*Berl. klin. Woch.*, No. 23, 1905) was able to demonstrate the Spirocheta pallida in the liver, spleen, inguinal glands, and the fluid from pemphigus bullæ, seven hours after death, in an infant dead of congenital syphilis. The same observer (*Berl. klin. Woch.*, No. 28, 1905) in two cases of superficial cancer and one cervical carcinoma found spiral organisms which were of considerable size and thickness and had few curves. He was unable to demonstrate the spirocheta pallida in these lesions.

Metschnikoff and Roux (*Bull. de l'Acad. de Med.*, May, 1905, p. 468) in six apes inoculated with syphilis found Spirocheta pallida in the initial lesions upon the genitalia in four. They further state their belief that its presence is diagnostic.

Zabolotny (*Roussky Vratch*, June 4, 1905) was able to isolate a spirocheta from the contents of enlarged glands and from excised papules of secondary syphilis. In thirteen of twenty-nine cases the organism was present. The glands contained only a few, while in the papules and roseola they were present in great numbers. In the smears from the glands peculiar rounded bodies staining light blue were found, the exact nature of which could not be determined. He seems to think that the Spirocheta pallida plays a part in producing the lesions of syphilis, but that as yet we do not know whether the organism represents a transition form of some parasite or whether it alone is the essential causative factor.

McWeeney (*British Medical Journal*, June 10, 1905) reports finding the parasite in enormous numbers in syphilitic lesions, and concludes that it may be etiologically connected with the disease. He further states that it seems important to make careful search for it in deeply situated lesions beyond the reach of surface contamination and to establish its absence in non-syphilitic ulcers of the genital tract.

Horand (*Lyon Medical*, February 21, 1904, p. 347) in the blood obtained from the arm vein of a syphilitic child found numerous active needle-like bodies undulating like spermatozoa. In initial lesions, bloodvessels, lymphatics, mucous patches, secondary and tertiary lesions, the following structures were observed: (1) Sporulated bodies, especially numerous in mucous patches; (2) colored granules which were very motile; (3) refringent bodies in the red globules and around them; (4) ameboid cells; (5) crescents; (6) needle-like forms or flagella darting in all directions; (7) bodies *en masse;* (8) bodies in rosettes; (9) isolated spheres; (10) a parasite in its stage of perfect development; (11) red globules containing granules; (12) white globules containing pigment. He concludes that the pathogenic agent of syphilis is a parasite of evolution, a protozoon, or better, a "hemoprotiste."

Vuillemin (*Compt. Rend. de l'Acad. des Sci.*, June, 1905, No. 23, cxl. p. 1567), in remarking upon the presumed agent of syphilis, proposes the name "Spironema pallida," for the spiral protozoon, with sharp ends, which differs from the trypanosomes in the appearance of the undulating membrane and its flagelliform prolongation. He claims that it is regrettable that the probable organism of syphilis called by savants Spirocheta pallida, should be presented to the public under that term, as this name was created in 1833 by Ehrenberg for the Spirocheta plicatilis. Further, he claims that the affinities of the organism should be sought in the direction of protozoa.

Levaditi (*Comptes Rend. de la Soc. de Biol.*, May 26, 1905), in two infants, congenital syphilitics, observed the Spirocheta pallida in the bullæ upon the hands and feet of one and in the liver and spleen of the other. He thinks that the disease, congenital syphilis, is a spirillosis presenting other points in common with recurrent fever in man and spirilloses of fowls, including geese.

Galli-Valerio and Lasseur (*Rev. Med. de la Suisse Romande*, July, 1905, p. 487), in several cases of syphilis exhibiting condylomata and mucous patches, found spirochetæ in the majority of instances. He states that the fact that the organism is not encountered in some cases does not speak against its specificity, because in a certain number Schaudinn personally found only a few organisms.

Mackenzie (*La Presse Med.*, May 27, 1905, No. 42, p. 340) asserts that in recurrent fever and syphilis ocular lesions are very frequent, and insists upon the difficulty of diagnosis between these maladies, as they are both spirilloses.

Jacquet and Sevin (*La Presse Med.*, May 24, 1905, No. 41, p. 338) were unable to identify the Spirocheta pallida in a great number of cases showing secondary and tertiary manifestations.

Hoffmann (*Berl. klin. Woch.*, June 5, 1905) found in the liver and spleen of a child dead of syphilis numerous Spirochetæ pallida, which were also present in the bullæ and inguinal glands. In papules distant from the lesions the organism was also found.

Flexner and Noguchi (*Medical News*, June 17, 1905, p. 1145) found the spirocheta in three cases of syphilis, while in two non-syphilitics they could not demonstrate the parasite.

Hexheimer and H. Hubner *(Deut. med. Woch.*, June 29, 1905, No. 26*)* in fifteen out of sixteen cases demonstrated the Spirocheta pallida; in one instance they identified it in sections of tissue. They failed to find them in syphilitic glands, in the blood, or in the organs of congenitally syphilitic children.

Kiolomenoglou and von Cube (*Munch. med. Woch.*, July 4, 1905, No. 27*)* discuss the occurrence of Spirocheta pallida in syphilitic lesions, but they consider it quite as important to confirm the absence of it in non-syphilitic lesions. They found the organism in a collection of syphilitic cases, in the secretion of an inflamed phimosis, in gonorrheal pus from an abscess of Bartholin's gland, in simple balanitis, in pus from a scrofulo-dermatitic abscess, in the degeneration products of a suppurating cancer and in tissue juice of condyloma acuminatum. Negative results were obtained in acute gonorrhea, syphilitic blood, acne vulgaris, impetigo, and phthisical sputum. They found the Spirocheta refringens in all the above cases as well as the Spirocheta pallida, and in addition numerous atypical organisms whose characters corresponded to neither of these. " It must be remembered that we have found Spirocheta pallida in stagnant secretions, as smegma, and the idea that it may also be saprophytic is not to be put to one side."

Rille *(Ibid.*, No. 29, 1905) found the Spirocheta pallida in six cases of syphilis; in three primary lesions in the male and one in the female, in a primary lesion of the coronary sulcus and in a papular efflorescence of the forearm.

Pflaeger *(Ibid.*, No. 29, 1905) claims that the organism is found in syphilitic tissue only; it is small, delicate, refractive, having pointed ends without flagella, occasionally nuclei or undulating membrane. He demonstrated the parasite in the blood of roseola, and noticed motility six hours afterward in salt solution, while this property was destroyed in from five to ten minutes in glycerin.

Jensen (*Deutsch. med. Woch.*, No. 30, 1905) found the organism in the fluid from a hard ulcer and lymph gland, two ulcerated and one non-ulcerated papules.

Raubitschek (*Wien. klin. Woch.*, No. 28, 1905) was able to demonstrate the parasite in the blood and the fluid of one broad condyloma. The blood was taken from the finger tips and stained by the ordinary methods.

Buschke and Fischer (*Vorgetragen in der Aerzte Gesellschaft des Krankenhauses am Urban*, May 11, 1905) found in spreads from the liver and spleen of a child dead of congenital syphilis the Spirocheta pallida, but were unsuccessful in demonstrating it in the living subject. In a later communication (*Deutsch. med. Woch.*, No. 21, 1905) they succeeded in finding the parasite in the blood during life. Babes and Panea (*Berl. klin. Woch.*, No. 28, 1905) in the blood of two cases of congenital syphilis were able to find the Spirocheta pallida, while in a third case no organisms were found in the blood, liver, or spleen. In the two positive instances it was also demonstrable in the mucous membranes, bone-marrow, thymus gland, conjunctival secretion, arachnoid fluid, lymph glands, liver, spleen, kidney, and adrenals.

C. Fraenkel (*Munch. med. Woch.*, No. 24, 1905) in six syphilitics was able to identify the Spirocheta pallida in all, and also saw the same organism in a non-specific lesion.

Spitzer (*Wien. klin. Woch.*, August 3, 1905) identified the organism in seven exanthemas, two ulcerated lesions, and in six cases of sclerosis; in non-ulcerated gummata, in mucous patches, and in non-specific lesions.

Wechselmann and Lowenthal (*Med. Klinik*, No. 26, 1905) observed motile spirochetæ in various specific lesions, and believes that it is important to find the organism in regions distant from the genitals.

Bandi and Simonelli (*Munch. med. Woch.*, No. 35, 1905) in examining a millimeter-sized plate of skin claim they found at the depth of these plates large cells with apparently degenerated protoplasm and containing the Spirochetæ pallida in their nuclear substance. They assert that this fact is very important and corresponds to what is seen in tuberculosis, leprosy, and glanders, that it is a true cell parasite and seems to show the nature of syphilitic lesions.

Omeltschenko (*Roussky Vratch*, July 23, *New York and Philadelphia Medical Journal*, September 30, 1905) in examining the scrapings of both hard and soft chancres, dry and moist syphilitic papules, and other granulating surfaces of a non-specific nature found in every preparation beautiful spirals of elastic tissue "which corresponded to the Spirocheta pallida and Spirocheta refringens." In every preparation the author purposely scraped the tissue of the corium. No typical difference of any sort could be detected between the spiral fibres and the organisms when stained with Giemsa's stain. In addition, the author examined the blood of syphilitics when condylomata were present, obtained by applying a leech and collecting the drops which exuded from the wound after the leech had been removed. In no case was he able to demonstrate spirochetæ.

Nigris (*Deut. med. Woch.*, September 7, 1905, No. 36) succeeded in demonstrating the Spirocheta pallida and refringens in the blood from a maculopapular efflorescence on the foot of a two months' old syphilitic child. In the serum from a blister over the eruption only the Spirocheta pallida was found.

Richard and Hunt (*Lancet*, September 30, 1905) remark that in the examination of "venereal sores" they found in films made from the scrapings the organism described by Schaudinn and Hoffmann. It appeared to occur in three forms, presumably involution forms of the same organism, differing only in thickness, length, and the number of spirals; one form being thick and straight or slightly curved, a second of the same thickness as the first, but with spirals; and the third exceedingly thin, distinctly spiral, with a large number of turns and very long. The first two varieties appeared to exist in the secretion and the superficial part of the sore, whilst the third variety occurred in the deep scrapings only. In three cases in the secondary stage with the rash of a few days' duration, stained films contained an organism like the fine one found in the sore. In one patient the organism was seen in the blood film taken on each of ten successive days, and in three cases in which the organism was found in the blood it had previously been seen in all forms in the primary lesions.

Fanoni (*Medical News*, October 7, 1905) reports upon five cases of syphilis in which he demonstrated the Spirocheta pallida in scrapings from chancres, condylomas, and papules.

Gordon (*American Medicine*, July 22, 1905) in eight specimens of cerebrospinal fluid obtained from cases of cerebrospinal syphilis was unable, except in a single doubtful instance, to demonstrate a spirocheta.

Metschnikoff (*La Presse Med.*, May 27, 1905, No. 423, p. 340) claims that syphilis is a chronic spirillosis due to the Spirocheta pallida of Schaudinn, is pathogenic to the human race, for the anthropoid apes, and for certain varieties of inferior monkeys or apes. He further states that the organism is not the same as the one found in the smegma of the prepuce or upon common ulcerations.

Tchlenoff (*Roussky Vratch*, June 18, 1905; *New York and Philadelphia Medical Journal*, August 12, 1905) studied fourteen cases of syphilis in which he examined the secretion of chancres, contents of inguinal glands and papules. In all specimens of hard chancres he found the Spirocheta pallida. He distinguished other spiral organisms, by their usually deeper staining properties and the smaller number of their spiral turns.

Schaudinn and Hoffmann recommend for staining the Spirocheta pallida azur eosin (Giemsa) made according to the following formula:

Azur No. 1	1 to 1000
Azur No. 2	8 to 1000

Eosin (water soluble) 2.5 of 1 per cent. sol. in 500 c.c. of water.

The staining mixture should be made up fresh as desired, and for this purpose 12 c.c. of the eosin solution are mixed with 3 c.c. each of azur No. 1 and No. 2. The material to be examined is spread upon a slide or cover-glass, fixed with absolute alcohol for ten to twenty minutes, and the stain applied for sixteen to twenty-four hours, it is then washed thoroughly in water, dried and mounted in balsam. Numerous modifications of this formula have been suggested, and Schaudinn, in a later communication, recommends one in which thirty-five drops of Grübler's Giemsa mixture are added to 20 c.c. of water.

Giemsa personally claims that the optimum time for staining with azur eosin is one hour. In another paper (*Deutsch. med. Woch.*, No. 2, 1905) Giemsa stains with azur eosin made with glycerin and methyl alcohol. After fixing in absolute alcohol he applies the stain for fifteen minutes. A better definition is claimed to be given to the organism if a 1 per cent. solution of carbonate of potassium is mixed with the water before the stain is diluted.

Gonder and Hoffmann stained the organism with fresh aniline gentian violet for twenty-four hours. Babes and Panea recommend the classic Romanowsky mixture applied for at least fourteen hours.

Davidsohn (*Berl. klin. Woch.*, No. 33, 1905) uses kreysl violet R, extra of Muhlheimer for from one to forty hours. He claims that the less manipulation indulged in the better the results.

Oppenheim (*Deut. med. Woch.*, No. 29, 1905) prepares a thin film of material on a cover-glass, dries in air, and without any further fixation applies an alcoholic solution of carbol gentian violet (5 per cent. watery carbolic acid 100 c.c.; concentrated alcoholic solution of gentian violet 10 c.c.). Heat is gently applied until steam arises then wash in water carefully, dry with filter paper and mount in balsam. Spirochetæ are stained blue.

Spitzer recommends Giemsa's azur eosin to be applied for six hours, and claims that it is harmful to permit it to remain too long, as the color becomes a faint green. Bandi and Simonelli obtained excellent results with Giemsa's azur eosin when allowed to act for from twelve to twenty-four hours, and were also able to demonstrate the parasite with Ziehl's carbol fuchsin.

McWeeney claims that with carbol fuchsin acting for an hour he obtained poor results, while with Giemsa's azur eosin the organism was stained a distinctly reddish violet. Bacteria in the preparation were stained blue.

Zabolotny after fixing in 5 per cent. solution of carbolic acid stained with azur eosin heated for fifteen minutes. Hexheimer and Hubner stain with Niblau B.R. or capriblau in 1 : 1000 aqueous solution for from sixteen to twenty-four hours.

Pflaeger used carbol gentian violet, without fixation, for one minute and washed in water, dried in air, and mounted in balsam. He claims that the spirochetæ are apparent under a magnification of 800 ocular No. 3.

Dudgeon (*Lancet*, August 19, 1905) demonstrated the organism with Leishman's stain as follows: A few drops of a 1 per cent.

solution of Leishman's powder in absolute methyl alcohol is placed upon the spread and allowed to fix and stain for thirty minutes, then add double the quantity of distilled water and stain for five minutes longer. Pour off excess and allow distilled water to act for one minute, remove the surplus and any precipitate with cigarette paper, dry and mount in balsam.

Reitman (*Deut. med. Woch.*, No. 25, 1905) recommends after drying the preparation in the air, fixing in absolute alcohol for ten minutes, water five minutes, 2 per cent. phosphotungstic acid, washing this off with seventy per cent. alcohol. The preparation is then stained with ordinary carbol fuchsin by heating over the flame until steam arises, wash in running water, pass through 70 per cent. alcohol and wash in water until no more color is given off. Dry and mount in balsam. The spirochetæ are stained intensely red, the nuclei dark and the protoplasm light.

Marino (*Annales de l' Institut Pasteur*, 1905, p. 761) makes up a mixture of methylene blue and azur as follows: Methylene blue 0.5 grm., azur 0.5 grm., water 100 c.c. Add an aqueous solution of carbonate of soda (5 per cent.) and after standing for twenty-four to forty-eight hours at 37° C. add an aqueous solution of eosin; filter and obtain the filtrate; dissolve 0.04 grm. in 20 c.c. of pure methyl alcohol. An eosin solution is made by adding 0.05 grm. to 1000 c.c. of water. Four drops of the first stain are applied to the cover-glass for three minutes, rocking the preparation constantly, then without washing in water apply eight to ten drops of the eosin mixture. Allow this to remain for two minutes, wash in water, dry and mount in balsam.

Bordet and Gengou stain with Kühnes' carbol methylene blue and follow with Nicolle's carbol gentian violet. Galli-Valerio and Lasseur stain with azur (Michaelis) for from nine to twelve hours after drying the preparation and fixing in the flame. They claim that the preparations stained with azur and mounted in balsam decolorize rapidly. Metschnikoff and Roux obtained excellent results by Giemsa's stain in from six to eight hours, by Marino's method, and with a solution of azur in methylic alcohol and a feeble solution of eosin.

L. Lesourd (*Ann. de Dermat. et de Syphilis*, June, 1905), after fixing the spread in ethyl alcohol for two or three minutes, dries and stains with Giemsa's mixture diluted in the proportion of one drop of the stain to 1 c.c. of distilled water and allowed to remain on the preparation from sixteen to twenty hours.

PERSONAL OBSERVATIONS. During the past four months the writer made studies of chancres, mucous patches, enlarged glands, condylomas, eruptions, and cerebrospinal fluid. The method of making preparations from the chancres and condylomas consisted in washing the surface with sterile salt solution and scraping the surface and deeper portions with a scalpel. Very little blood was seen in any film, the few cells observed being mostly lymphocytes. Sterile salt solution was mixed with the material from glands and with the serum from the eruptions for study in the fresh condition. The material from the glands was obtained by means of a hypodermic syringe, which was plunged into the organ and a few drops of fluid withdrawn. The serum from the eruptions was secured by means of raising a blister, using either ammonia or chloroform upon absorbent cotton, and then covering with a small glass receptacle, which was used as a dry cup (as is done by Dr. Wilson). Or, in the later cases the skin was pinched up by means of a dressing forceps (as suggested by Dr. Coplin), held until blanching occurred, then a small incision was made and a drop or two of pure serum was collected in a capillary glass tube.

A small drop of the material, whatever the source, was placed upon a cover-glass, inverted upon a slide, the edges sealed with vaselin and examined in the fresh condition. The sediment obtained by centrifugalization of the cerebrospinal fluid was examined in the same way. In some specimens of fluid no sediment was obtained after several hours' centrifugalization.

Very good preparations were obtained with Wright's blood stain, with dilute carbol fuchsin, with Jenner's and with Romanowsky's blood stains. The best results were obtained with Giemsa's azur eosin, in the strength as first proposed by Schaudinn and Hoffmann.

Fixation was accomplished with absolute alcohol or 95 per cent. alcohol, used for ten to twenty minutes, and thirty minutes to twenty-four hours application of the stain was the usual routine. It was found, however, that just as good results were obtained in fifteen to thirty minutes as in twenty-four hours. The preparation must be thoroughly washed in water, as incomplete washing tends to throw down needle-like crystals. With carbol gentian violet no satisfactory preparations were observed.

In the fresh state the Spirocheta pallida was very difficult to see. The most common movement described by the parasite was bending of the whole organism backward and forward, or what may be described as quite a marked vibratory thrill. Occasionally a parasite could be seen attached to a red blood cell or a lymphocyte, and in one specimen an organism was present upon a long bacillary-like body. The pointed ends of the parasite were quite distinct, and the number of bends or curves varied from three to eight. In the stained spreads by Wright's method the spirocheta was colored a faint purple while the Spirocheta refringens was stained a deep purple. No matter what stain was used or how long applied the Spirocheta pallida was exceedingly faint, and in some preparations the parasite could just be made out after a long and very careful search. In all preparations the organisms were extremely few, and no more than five were seen in any one field of the one-twelfth oil-immersion lens. On the other hand the Spirocheta refringens was comparatively abundant and could be made out without any difficulty. In the fresh as well as the stained preparations one could be easily misled, many times, by shreds of fibrin or mucus taking on very fantastic shapes and outlines and resembling very closely the spirochetæ, both large and small.

In all, thirty-four cases of syphilis were examined. There were ten chancres; eleven mucous patches (ten from the mouth and one from the rectum); four enlarged glands; three condylomas and six eruptions. As the disease is regarded as a spirillosis by some observers, the cerebrospinal fluid from fourteen cases was examined. From most of these specimens no sediment could be obtained for study. The greater number were obtained from cases of cerebrospinal syphilis, while the remainder were from patients in the eruptive stage of the disease. In every specimen of material examined, with the exception of cerebrospinal fluid, the Spirocheta pallida was demonstrable. Attempts to cultivate the Spirocheta pallida upon fluid human blood serum in aerobic and anaerobic conditions were entirely without result. The serum was incubated for three weeks at 37° C. The method of procedure was to draw blister serum in a capillary tube from a known healthy person, add a drop or two of serum from a blister over the eruption of a syphilitic, seal the tube in the flame or plug with cotton, and incubate.

As control cases, preparations were made from diseases which were not specific in nature and included chancroids, eczema, psoriasis, balanitis, enlarged glands other than syphilitic, bone-marrow, spleen, and liver of a child supposed to have died from congenital syphilis; serum from blisters in healthy subjects, material from a case of scarlet fever; two non-specific ulcers of the penis, and an ulcer of the tongue. In none of these conditions was any spiral organism observed.

In two ulcers of congenital syphilitic origin, one in a child aged two years the other in a girl aged sixteen years, no spiral organisms were seen. In the blood from several cases, obtained from the finger and also from the vein of the arm, the examinations gave negative results as to the presence of the Spirocheta pallida.

In the examination of a mucous patch from the mouth so many spiral organisms were encountered of various sizes that a number of controls from healthy mouths were studied. To this end scrapings from the buccal mucous membrane and from the margin of the gums and teeth were collected from forty-seven persons in good health. In thirty-six at least two forms of spiral organisms were plainly seen. One form almost constantly present was similar to the Spirocheta refringens; a second variety was short, stained rather faintly, had from two to four curves, pointed ends, and was slightly thicker than the Spirocheta pallida. The third form was a very long, thin, faintly staining spiral, sometimes with a loop formed in its length, and pointed ends. Another form, constituting a fourth variety, could not be differentiated from the spirilla observed in Vincent's angina. This spirillum was, however, present in only a few cases.

In another series of controls the mucous membrane scrapings were obtained from twenty inmates of the women's venereal ward, suffering from diseases other than syphilis. In all these specimens an organism was found corresponding to the Spirocheta refringens.

while in 80 per cent. a palely staining spiral was present which could be differentiated from the pallida in being slightly thicker and not possessing such decidedly pointed ends. The Spirocheta refringens, however, resembled the one found associated in syphilitic lesions. In one chancre spirals were encountered which stained faintly but were too long for the Spirocheta pallida, being at least thirty to forty microns in length, five-tenths of a micron in thickness, and possessing pointed ends.

The organisms are more abundant in the early days of the appearance of any lesion. Upon several occasions, when four or five organisms were found in a field, a second preparation made later from the same situation, though the patient received no local treatment, yielded only one or two parasites to a cover-glass, and in some cases none could be found.

It is the writer's opinion that the Spirocheta pallida properly belongs with the animal parasites and is a protozoon. At no time was an undulating membrane demonstrated as in trypanosomes.

That it plays some part in the etiology of syphilis seems plausible, as it has not been encountered, except by one or two observers, in any other lesion than syphilis. The probable reason that the organism was not demonstrable before, is on account of its extreme minuteness; the difficulty attending its coloration, and its scarcity in some of the lesions and preparations.

I wish to express my most sincere thanks to Dr. John D. Wilson for extremely valuable assistance in the collection of material and study of cases, and also to Drs. Dean, Dodge, and Smith, of the Philadelphia Hospital, for obtaining material upon different occasions.

October 26, 1905.

Meningomyelitis with Intense Swelling of the Spinal Cord and of the Roots of the Cauda Equina.

By WILLIAM G. SPILLER, M.D.

AND

EVA RAWLINGS, M.D.

H. L., a boy, five years of age, was admitted to the University Hospital, service of Dr. C. H. Frazier, March 30, 1905, having symptoms of meningitis. With the exception of an attack of measles and mumps he had always been healthy. There was no family history of tuberculosis. Three weeks before admission the child had fallen from a chair, striking his forehead rather hard. After the fall he had lost in weight, and was subject to attacks of acute headache, more marked on the right side, and occurring every three or four days. Two months after the fall he developed an internal strabismus of the left eye, and a week later he had a slight convulsion. A week after the convulsion there was a bloody discharge from the nose, lasting twenty-four hours. No evidence of ethmoidal disease was found. On the three days preceding his admission to the hospital he suffered with convulsive attacks, which were confined chiefly to the left side of the face, with occasional twitching of the fingers of the left hand. These occurred about three times a day.

On admission the child was in a stuporous condition. He lay on his back with his head turned toward the right, and the knees and thighs partly flexed. He could be easily aroused, answered questions rationally at times, but was often greatly confused. The pupils were equal, widely dilated, and sluggish. Low-grade double optic neuritis was present, greater upon the right side. There was paralysis of the left external rectus. The tongue was protruded tremulously with decided deviation toward the right. Some rigidity of the posterior neck muscles existed, with tenderness along the spine. The abdomen was soft, relaxed, and scaphoid. Kernig's sign was present on both sides, more marked on the right. The knee-jerks were diminished. Temperature 97°, pulse 100, respiration 24. While being examined he suddenly lost consciousness.

He lay perfectly quiet with eyes partly closed, and could not be aroused. All the muscles were flaccid, with no twitching of any part. His pulse was strong but irregular; respiration irregular, the child taking a long breath and then none for a considerable time. In about five minutes he gradually regained consciousness, was confused for some time, and complained of headache.

Lumbar puncture was performed, one ounce of cloudy fluid being drawn off. On April 5th tuberculin was administered, with a suggestive reaction. The patient gradually improved. Tuberculin was again administered on April 11th, the patient responding to the test. By the 14th his general condition seemed to be growing worse, the child becoming more stupid. Kernig's sign became more marked and double Babinski sign appeared. A mild keratitis and conjunctivitis of the right eye developed. On the 18th lumbar puncture was again performed and fluid to fill two test tubes, cloudy and slightly bloody and under considerable pressure, was withdrawn. After puncture his general condition improved, but by the 21st he again grew worse. Vesicles appeared along the distribution of the supraorbital nerve. There was a constant involuntary opening and closing of the eyelids. The temperature fluctuated widely.

During the succeeding week he lost ability to swallow and nutritive enemata were employed. He lay in a comatose condition most of the time. On the 28th lumbar puncture was again performed and fluid distinctly more cloudy was withdrawn. He improved slightly, but gradually grew worse, dying on May 5.

The necropsy, performed by Dr. Allburger, revealed internal hydrocephalus and intense meningitis over the base of the brain. The spinal cord was greatly enlarged throughout with softening in the interior in places. Numerous nodular swellings were found on the roots of the cauda equina, much resembling multiple fibromata of the spinal cord. Tuberculosis of the viscera was not found.

On microscopic examination there was found an intense infiltration of mononuclear cells in the pia, spinal cord, pons, chiasm, optic nerves, and paracentral lobules. Numerous cavities developed in the cord during the process of hardening. The spinal pia was greatly thickened everywhere. No distinct degeneration of nerve fibers could be seen by Weigert's hematoxylin or the acid fuchsin method. The nerve cells of the anterior horns appeared possibly a little swollen, stained diffusely by acid fuchsin, the nucleus being usually in the center of the cell. In certain parts of the thoracic region the cellular infiltration was intense and formed distinct circumscribed accumulations in the posterior columns. At other parts of the cord dense masses of cells were seen extending from the periphery into the cord. The greatly thickened roots of the cauda equina showed nerve fibers separated from one another, so that in transverse sections, on hasty examination only, they presented the appearance in places of cells, the axis cylinders resembling the nucleus. Tubercle bacilli could not be found in the spinal cord or elsewhere.

The most important findings in this case were the intense swelling of the cord, and the nodular enlargements of the roots of the cauda equina caused by cellular infiltration and swelling of the tissues. *November* 9, 1905.

Observations upon the Phagocytic Power of the Blood of Normal Human Beings.

BY JOSEPH McFARLAND, M.D.,

AND

EDWARD M. L'ENGLE, M.D.

(PRELIMINARY REPORT.)

IN 1902 Leishman devised a method of quantitatively estimating the phagocytic power of the leukocytes of the blood. (*British Medical Journal*, January 11, 1902, vol. i. p. 73.)

This method was considerably improved upon by Wright and Douglas in a paper entitled "An Experimental Investigation of the Role of the Blood Fluids in Connection with Phagocytosis," and the technical procedures contained in these two papers have been employed by us with such modifications as will be described below. The study of "*opsonins*," begun by Wright and Douglas, and of late pursued by numerous observers, seems destined to become of practical clinical importance; and it was with the object of determining such variations as might obtain in the phagocytic power of unmodified bloods preliminary to an investigation of opsonins that the observations contained in this paper were made. It seemed to us that before any accurate experimental studies could be made it would be necessary to determine the variability or invariability of the behavior of the blood corpuscles of different supposedly healthy individuals, so that in future experiments we would be informed as to the possibility of drawing correct inferences from the behavior of the cells from one individual as compared with those of another individual.

It has been our ambition to make the entire technique sufficiently simple to be performed in a clinical laboratory by anyone possessing a small amount of technical ability.

In order to perform the experiment it is necessary to have, first, the living phagocytic cells, and second, the bacteria that they are to take up; and it is necessary to bring these two into contact under invariable conditions, in order that correct deductions concerning their interaction may be drawn.

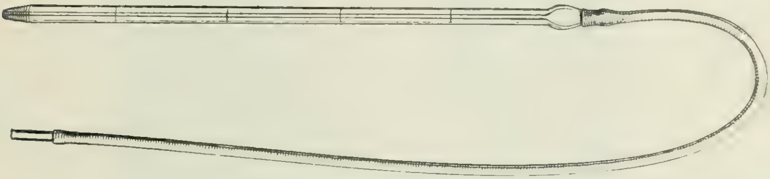
SECURING THE PHAGOCYTIC CELLS.—With the minute quantities of blood obtainable from an ordinary puncture in the finger it is inexpedient as well as unnecessary to attempt to separate the leukocytes from the other blood cells ; and as the red corpuscles and the non-phagocytic lymphocytes do not in any manner affect the activity of the phagocytic white cells distributed among them, they can be permitted to remain, no attention being paid to them in the final microscopic examination. Moreover, by having these elements present there may be more nearly perfect correspondence between that which goes on *in vitro* under the conditions used and that which takes place *in vivo* during infection.

The first difficulty that has to be overcome is the undesirable coagulation of the blood, which by entangling the corpuscles in the crysomentum makes it impossible for the bacteria to be brought into uniform contact with them. Two methods can be utilized for this purpose—defibrination of the blood, as is commonly employed in hemolytic investigations, and decalcification, as recommended by

Wright and Douglas. It might be suggested that decalcification, by the addition of sodium citrate, naturally brings about an abnormal chemical condition of the blood; and it is quite proper to inquire at once whether this variation will have any bearing on the activity of the phagocytes and their attitude toward bacteria. This was carefully investigated by Wright and Douglas, who found that the addition of the necessary quantity of citrate of sodium had no influence whatever upon the behavior of the blood corpuscles.

To secure the citrated blood, we make use of a very simple pipette, easily made in the laboratory in a few minutes, and perfectly satisfactory so far as our experience goes. It consists of a thermometer tube about six inches long, with a caliber of one millimeter, drawn out in the flame of a blow-pipe so that it is pointed at one end where it is to contact with the drop of blood and narrowed and rounded at the other for the attachment of a small rubber tube. The rubber tube should be sufficiently long to enable one to work conveniently with the pipette while the end of it is held in the mouth, and it should have a short glass mouthpiece so that it can be quickly closed by the tongue. Enough mercury is sucked up into the tube to form a column about five centimeters in length. The finger is then used to close the end of the pipette so the mercury cannot escape. A mark is then made at the upper end of the column of mercury, the tube held horizontally, the finger released from the end of the pipette, and the mercury coaxed by gentle tapping into a position where its lower end corresponds to the mark where the upper end originally stood. A second mark is now made at the upper end of the column, thus giving us two segments of the pipette of exactly the same capacity. We have not

FIG. 1



Pipette for making the mixture of blood and citrate of soda solution.

found it necessary to determine the cubic contents of these segments, as it is immaterial for the purpose for which the tube is intended. The mercury is now expelled and the tube is ready for use.

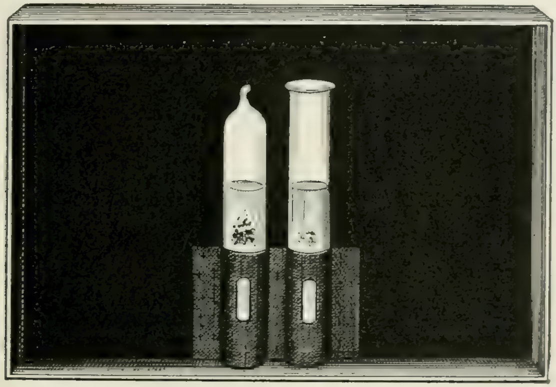
To prevent the coagulation of the blood a 1 per cent. solution of sodium citrate in an 0.85 per cent. solution of sodium chloride is employed. In using the pipette the column of the citrate of sodium solution is carefully sucked up until the first mark is reached. By using the pipette in a horizontal position it is not difficult to stop the flow of fluid at any desired point, by closing the end of the rubber tube with the tongue. The pipette is next applied to a drop of blood drawn from one side of the ball of the thumb, and the blood is sucked in until the citrate solution, ascending in advance of it, reaches the second mark. The end of the pipette is then wiped off and the contents blown out into some small glass receptacle, and sucked up and blown out of the pipette once or twice, in order to secure thorough mixing. The blood is then ready for admixture with the bacteria.

The bacteria used in all of our experiments were staphylococci, and we soon found, as our predecessors had done, that it was essential to bring into contact with the corpuscles uniform quantities of the bacteria in order that uniform results might be obtained. Our method of securing this uniformity was, however, very different from that of Wright, who enumerated the bacteria (*Lancet*, July 5, 1902). This seemed to us a rather tedious procedure, and one the difficulty of which so complicated the technique that the accuracy did not compensate for the expenditure of time and labor. The necessity for using standardized bacterial suspension is easily determined, and our experiments show the variation in the number of bacteria taken up by the leukocytes to vary with almost mathematical certainty according to the dilution employed. Thus, a suspension of bacteria was made, a portion diluted with an equal volume of physiologic salt solution, a portion of this further diluted with an equal volume of salt solution, and a portion of this still further diluted with an equal volume of salt solution. We thus had four suspensions, representing one-half, one-fourth, and one-eighth the original number of bacteria. The counts were as follows:

Original suspension	8.375
First dilution (through an accident we were unable to count the bacteria contained in this specimen.)	
Second dilution	4.7
Third dilution	2.85

It occurred to us that uniformity in the number of bacteria in the suspensions employed could be secured with reasonable accuracy by some means of measuring and standardizing the turbidity of the fluid containing them. We therefore devised a simple instrument for which we suggest the name *nephelometer* (νεφέλη, mist, cloud, fog), by which it became easy to secure any desired degree of turbidity. We first prepared a 1 per cent. solution of barium chloride, second, a 1 per cent. solution of sulphuric acid in distilled water. Then from these we made ten solutions of the sulphuric acid, using respectively 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 per cent. of the barium chloride solution. These gave us ten different precipitates to be used as turbidity standards. About three cubic centimeters of each was placed in a small test tube, and the top sealed in the blow-pipe flame. With the aid of a box-lid and a strip of stiff linen we next prepared a holder into which the tube containing the desired precipi-

FIG. 2

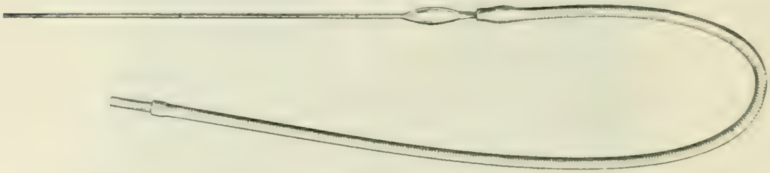


The nephelometer. The standard of turbidity is contained in the sealed tube on the left and the bacterial suspension in the open tube on the right made to correspond by the addition of more bacteria if too thin or more salt solution if too dense. The comparison is made through the small fenestra against a white cloud tate could be stood for comparison with the tube of salt solution in which the bacteria were to be suspended, the comparative turbidity of the two being observed through small slit-like orifices against a bright sky or preferably a white cloud. We have found that *the tube containing 5 per cent. of barium chloride corresponds to the most useful bacterial suspension.*

The bacteria were always secured from twenty-four-hour-old agar-agar cultures, which we found it easy to mix in homogeneous suspension with the physiological salt solution.

As recommended by Wright and Douglas the contact of the citrated blood containing the phagocytes with the bacterial suspension was permitted to take place in capillary glass tubes prepared for the purpose by drawing out an ordinary piece of glass tube in a blow-pipe flame until it was about the diameter of a lady's hatpin.

FIG. 3



Capillary tube for marking the citrated blood and bacterial suspension.

Slight variations in the diameters of these tubes are unimportant, though Wright and Douglas have shown that great variations, as, for instance, between tubes several millimeters in diameter and tubes of hair-like fineness, cause variations in the results obtained. It seems unnecessary to calibrate these capillary tubes with mercury. The portion of the tube to be used, being about fifteen centimeters in length, should be uniform to the eye. The caliber is then fairly uniform throughout. With a blue pencil one makes a mark upon the tube about five centimeters from its end and a second mark five centimeters above. A small rubber tube is attached to the upper end of the tube, which may be narrowed for the purpose, and the citrated blood is drawn up to the first mark. The bacterial suspension is now drawn in until the contained fluid reaches the second mark. If the glass tube from which the capillary tube was made have a caliber greater than three millimeters, it may not be found possible to mix these two solutions in the pipette; and it will then be necessary to blow them out upon a glass slide with a concavity, drawing them into the pipette and blowing them out once or twice to secure their mixing. After mixing, the fluid is drawn into the capillary portion of the tube, the end of which is sealed in a flame. The mixture of citrated blood containing the leukocytes and the bacteria must now be placed for some time in the thermostat at 37° C., at which the human leukocytes become active and phagocytosis takes place.

Striking variations in the results obtained may arise from inattention to the length of time that the phagocytes are allowed to remain in contact with the bacteria. This is shown by the following experiment, in which preparations made as described were examined after thirty and sixty minutes' sojourn at a temperature of 37° C.:

HUMAN BLOOD AND SUSPENSION OF STAPHYLOCOCCUS PYOGENES AUREUS

	Thirty minutes	Sixty minutes.
A B C	11.67	26.725
B	7.2	7.6
S	15.6	24.25
C	7.75	10.425

When the duration of the exposure exceeds thirty minutes the number of contained bacteria becomes so great as to interfere with the successful count of the bacteria contained in the leukocytes. On this account we have uniformly exposed our mixtures for thirty minutes. Doubtless the phagocytes are active at temperatures less than 37° C., but as we are endeavoring to approximate *in vitro* what takes place *in vivo*, and as in every well-equipped laboratory an incubator is always running at 37° C., our experiments have all been performed at that temperature. At the end of this time it will be observed that sedimentation of the blood corpuscles has taken place to one side of the capillary tube. This shows the importance of laying the tube upon its side instead of standing it upon end, and also shows the importance of mixing the contents by whirling the tube between the fingers for a minute or two before discharging them.

Method of Enumerating the Bacteria and Estimating the Phagocytic Power of the Blood. The slides and cover-glasses employed should be cleaned with sulphuric acid, water and alcohol, in order that they may be free from grease and other impurities. When the half-hour has expired and the time has come for the bacteria to be enumerated the end of the capillary tube is broken off and sufficient of the contents of the tube is discharged upon a clean cover-glass to enable one to prepare a satisfactory film by the ordinary method of superimposing a second glass and sliding it off. After drying in the air without the application of heat the specimen is stained by some method that will enable one easily to differentiate the varieties of leukocytes and distinctly see the bacteria they contain. Of the various methods for staining the blood we have found that of Marino (*Annales de l'Institut Pasteur*, 1904, vol. xviii. p. 761) to be most satisfactory, in which the following solutions are employed:

Solution No. 1.

Methylene blue	.5 gr.
Azur II	5 gr.
Water	100.0 gr.

Solution No. 2.

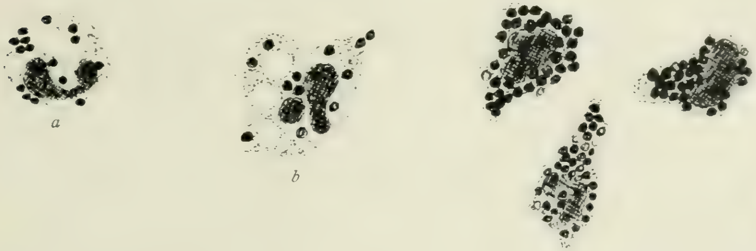
Carbonate of soda	.5 gr.
Water	100.0 gr.

These two solutions are mixed and allowed to remain in the thermostat at 37° C. for forty-eight hours. At the end of this time a 0.2 per cent. solution of eosin in water is added and the fluid is filtered through paper. The precipitate, after drying in the air, is dissolved in pure methyl alcohol in the proportion of 0.04 gram of precipitate to twenty cubic centimeters of alcohol. This is the stain.

For differentiation a 1 : 10000 eosin solution is employed.

Directions for Staining.—The cover-glass upon which the film is spread is held in an appropriate cover-glass forceps. Four small drops of the blue solution are allowed to fall upon it from a dropping bottle and permitted to act for exactly three minutes; the methyl alcohol fixes the film to the glass. Then without washing add from eight to ten drops of the eosin solution and allow it to act for exactly two minutes, during which time the staining takes place. The fluid is poured off and the preparation quickly washed in distilled water, dried, and mounted in Canada balsam. Properly prepared specimens show the erythrocytes to be stained a faint transparent green color. The cytoplasm of polymorphonuclear leukocytes is almost hyaline and has a faint pink color. The nuclear structure is beautifully shown and the contained bacteria stand out clearly, their color being brilliantly blue. The eosinophile cells show the oxyphile granules stained a brilliant red color. The small lymphocytes are brilliantly blue. The large lymphocytes show a transparent nucleus and a hyaline cytoplasm of a pink color which varies in intensity. The blood platelets are distinct, occur in small groups, and are violet in color and granular in appearance.

FIG. 4



Leukocytes containing staphylococci: *a* and *b*, after thirty minutes' exposure; *c*, after sixty minutes' exposure, according to the method described, at 37° C

The bacteria will be found scattered over the entire field, varying numbers of them being taken up by the polymorphonuclear leukocytes and a few by the large lymphocytes.

METHOD OF ENUMERATING THE CONTAINED BACTERIA.—The use of a mechanical stage renders the enumeration of the bacteria more easy and certain, though it is in no sense indispensable. We are in the habit of counting the number of bacteria in the first twenty polymorphonuclear leukocytes observed and then averaging. In all our examinations we have made two enumerations. The exact method of doing this varies according to the condition of the spread blood, but other things being equal the first count is made upon cells contained in the upper left-hand fourth of the cover-glass and the second enumeration upon cells in the lower right-hand fourth of the cover-glass. We have also endeavored to have each enumeration of twenty cells done by a different observer, so that personal equation might be eliminated.

ORIGINAL OBSERVATIONS. By these methods we have now studied the bloods of twenty-four supposedly healthy individuals, all of whom were students or laboratory workers, with the following results:

Synoptical table showing the relation of the phagocytic action of the leukocytes of supposedly healthy persons toward staphylococci.

CLASS I. Positive history of past or present disposition to suppuration. All of these persons are well at present and have no lesions.

	Acne.	Furuncles.	Carbuncles.	Appendicitis	Pneumonia.	Abscess.	Gonorrhœa.	General health.	Phagocytic count.
Prk	+	24 or more remembered.	Remembers. 1.	0	0	0	0	Excellent.	5.55
Sml	0	Numerous.	Many, some within a year.	0	0	0	0	Good.	4.65
Sth	0	Numerous.	0	0	?	0	0	Good.	4.125
Opf	0	7 or more.	0	0	0	0	0	Has boil on neck and asthma.	11.25
Crl	+	Numerous.	0	0	0	1 on ankle.	0	Excellent.	9.7

5)35.275

Average 7.055

CLASS II. Vague Past History of Suppurations.

	Acne.	Furuncles.	Carbuncles.	Appendicitis.	Pneumonia.	Abscess.	Gonorrhœa.	General health.	Phagocytic count.
Hfm	0	A few 15 years ago.	0	0	0	0	+	Good since typhoid.	10.7
Dmd	0	0	0	0	0	1 seven yrs. ago	0	Good.	14.
Cst	0		0	0	0	0	0	0	12.65
Cll	0	0	1 long time ago.	0	0	0	+	Excellent.	6.2
Bkn	0	+ some time ago.	0	0	0	0	0	Excellent.	7.2
Chtn	0	+ some years ago.	0	0	0	0	+	Excellent.	7.75
Stn	0	+ twenty years ago.	0	0	?	0	0	Good.	11.8
Bus	0	0	0	0	0	0	+	Excellent.	8.2

8)78.90

Average 9.81

CLASS III. No history of any suppuration

	Acne.	Furuncles.	Carbuncles.	Appendicitis.	Pneumonia.	Abscess.	Gonorrhœa	General health	Phagocytic count.
Bkz	0	0	0	0	0	0	0	Excellent.	13.57
Ptr	0	0	0	0	0	0	0	Excellent.	12.57
Rch	0	0	0	0	0	0	0	Excellent.	9.75
Glhr	0	0	0	0	0	0	0	Excellent.	11.3
Shn	0	0	0	0	0	0	0	Excellent.	15.6
Dlg	0	0	0	0	0	0	0	Excellent.	15.71
Mzt	0	0	0	0	0	0	0	Excellent.	9.67
Hks	0	0	0	0	0	0	0	Excellent.	23.125
Hlv	0	0	0	0	0	0	0	Excellent.	19.2
Bky	0	0	0	0	0	0	0	Excellent.	11.67
Dey	0	0	0	0	0	0	0	Excellent.	23.2

11)170.365

Average 16.39

From these observations it becomes evident that there is no normal standard of phagocytic energy for supposedly healthy individuals, but that the corpuscles of different individuals supposedly in perfect health vary between 23.2 and 4.125.

It seems to us that these results have a direct and important bearing upon the subject of *opsonins*, and their variation in health and disease. Wright and Douglas, who first employed the term "opsonins" (Latin, *opsono*, I cook, I prepare pabulum for), consider them to have important clinical importance, and much work has already been done by workers in various countries in investigating them, especially in relation to tubercle bacilli and tuberculosis.

Opsonins may be defined as substances in the blood serum which act upon the bacteria, preparing them for phagocytosis. Washed leukocytes brought in contact with bacteria normally taken up by them fail to manifest any phagocytic action. Washed leukocytes suspended in heated serum also fail to take up bacteria, so that the whole process of phagocytosis seems referable to the preparation of the bacteria by thermolabile substances contained in the serum.

In all the recorded experiments the opsonic power of the blood, or "opsonic index" is determined by comparison with "normal blood," but our observations indicate that so far as the staphylococcus is concerned the normal variations are too wide to enable many conclusions to be drawn. It would seem to be impossible to establish a general standard of comparison corresponding to "normal blood," and it seems to us that the only satisfactory method of making comparative *opsonin* observations would be by comparing the various readings—a given blood with one another.

We hope to make *opsonins* the subject of a further communication.

We have been able in two cases only to repeat these counts upon different days. Thus, the phagocytic index of the leukocytes of Stm. was enumerated at five days' interval, the first enumeration yielding the result 15.6 and the second 9.95. On the day the second enumeration was made, Stm. was taken ill with a mild attack of influenza. The blood of Prk. was examined at a similar interval, the first count being 5.55, the second 5.22. Here in one case there is a distinct variation, in the other a remarkable uniformity. It has been pointed out (Meakin and Wheeler, *British Medical Journal*, November 25, 1905, p. 1396) that the opsonic index of the blood varies at different times during the day, apparently according to the activity of the individual; and lest it might appear that we had been inattentive to this detail, we wish to state that all of our experiments have been made between the hours of three and five in the afternoon.

It was our hope to give these observations some practical clinical bearing, and the continuance of our work will be in the direction of studying the phagocytic index of the blood in various morbid conditions. It is interesting to note what remarkable correspondence there is between the phagocytic index and the history of suppurations in cases tabulated.

CONCLUSIONS. 1. Leishman's method of determining the phagocytic power of the blood, as modified by Wright and Douglas and by ourselves, is a very simple method adapted to clinical application.

2. Marino's stain is very satisfactory for demonstrating the leukocytes and the contained bacteria.

3. There is no uniformity in the phagocytic indices of the bloods of supposedly healthy individuals.

4. The phagocytic index of the same individual may be constant, or it may vary upon different days, according to the health of the individuals.

5. An exceptionally low phagocytic count usually indicates a present or past predisposition to suppuration (the phagocytic index in this regard being determined by the use of staphylococcus pyogenes aureus).

6. The phagocytic index may not be below the average in all cases in which there has been a tendency to suppuration.

7. The wide variation from the phagocytic index of supposedly healthy individuals seems to indicate that for staphylococci, at least, there must be equally wide variations in the "opsonic index."

8. Such variation in the opsonic index suggests the impossibility of establishing any other standard of comparison than the blood of the patient himself.

January 28, 1906.

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Pulmonary Edema, with Analysis of 405 Cases Occurring in 2030 Autopsies.

BY W. M. L. COPLIN, M.D.

(From the Laboratories of the Jefferson Medical College Hospital.)

WRITERS on systemic medicine, and I would include also those who have written volumes devoted to diseases of the lungs, usually give but little space to the consideration of pulmonary edema. The neglect of this important condition may be attributed to a number of factors. In the first place pulmonary edema is rarely, if ever, an independent affection; it usually constitutes a part of, or is superimposed on, some other condition the relief of which is followed by the disappearance of the concurrent edema. A second important factor determining the manifest neglect of this interesting subject is the commonly accepted belief that the process is essentially agonal and that patients get pulmonary edema because they are dying and not that pulmonary edema is the cause of death. That this belief is not justified is shown by the fact that the condition is absent in 80 per cent. of the bodies examined postmortem; of 2030 autopsies—the analysis of which constitutes the statistical basis of this paper—

in but 405 (less than 20 per cent.) was there pulmonary edema of sufficient intensity to attract attention. In addition to its inconstant occurrence there is the further fact that it may be unilateral; an analysis of the 405 cases shows that in 18 the right lung was involved, in 14 the left lung, and in the remainder both organs. Certainly, the influences of the death agony must be exerted on both sides, and, therefore, the occurrence of unilateral pulmonary edema should be regarded as against a belief in the agonal nature of the affection. My statistics are not entirely in accord with those of Owen,[1] who found that in 228 consecutive autopsies, 124 showed edema of both lungs and in 8 one lung only was affected. For the foregoing and other reasons, to be given later, I venture to oppose the suggestion of Cohnheim[2] that "a man does not die because he gets edema of the lung, but he gets edema of the lung because he is on the point of dying."

There are certain fairly distinct forms of pulmonary edema that should be recognized. The condition may be local or diffuse, unilateral or bilateral, primary or secondary. The local circumscribed or focal edema of the lung may be briefly dismissed; it is commonly observed around inflammatory processes, abscesses, infarcts, neoplasms and cysts, and in such conditions is attributable to the direct influence of limited circulatory disturbances and to the action of diffuse toxic substances engendered by the pre-existing lesion. Terminal edema incident to prolongation of the agonal period partakes of the characters of a local lesion, is manifestly favored or intensified by gravity, and is always more marked in dependent portions of the organs. Associated congestion due to flagging heart and the imperfect pulmonary ventilation resulting from enfeebled or narrowed pulmonary excursion are important causal factors. This type of pulmonary edema possesses little significance independent of the affection with which it occurs. The symptoms presented are attributable to the primary affection, and it is not established that the edema unless extensive, exerts any important influence in determining the ultimate outcome of the case.

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[1] Brit. Med. Journ., January 2, 1904, p. 1.

[2] Lectures on General Pathology, Sydenham Translation, 1889, p. 528.

Diffuse or general pulmonary edema was recognized by Laennec[1] in 1819, more accurately described by Andral[2] in 1837, and carefully studied by Legendre[3] in 1846. Rokitansky[4] describes pulmonary edema as an inundation of the parenchyma with thin serous transudate occupying the air vesicles. The affection has also been termed serous apoplexy of the lung, serous infiltration of the lung, and pulmonary dropsy. The condition has been produced experimentally by the injection of water (Sahli also Cohnheim[5]), muscarine (Grossmann),[6] prussic acid (Sahli), salicylate of methyl (Chatin and Guinard), amyl nitrite (Winckler), by compression of the left ventricle (Welch),[7] and more recently by the injection of adrenalin (Bouchard and Claude,[8] and Meltzer[9]). The quantity of adrenalin necessary to induce edema clearly varies, and different animals manifest different degrees of susceptibility. Josué states that for a rabbit weighing from 2 to 2.5 kilos, six drops is sufficient; Meltzer has observed fatal pulmonary edema after comparatively large doses (1.5 c.c.). The smallest dose that I have seen kill is 0.7 c.c. in a rabbit weighing 1500 gms. The phenomena in these experimental cases are that immediately upon receiving the injection a rapidly progressing dyspnœa appears, the animal seems to be weak, frequently falls on one side, the respirations become more and more shallow, and mucus—at first clear, later rose colored—escapes from the nose and mouth; convulsions are occasionally observed Postmortem the lungs and bronchi show the changes usually observed in the acuter forms of pulmonary edema in man. Pokrowsky[10] has observed pulmonary edema following experimental carbon monoxide poisoning of rabbits. Friedlander[11] found that clamping or ligating the aorta between the heart and the innominate, produced pulmonary edema.

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[1] De l'Auscultation médiate, 1819, vol. ii.

[2] Commentaires a la 4e edition de Laennec, 1837.

[3] De l'oedema aigu du tissue cellulaire du poumon qui succède a la scarlatine, 1846.

[4] Lehrbuch der path. Anat., 1861, Bd. iii, p. 63.

[5] Arch. f. exper. Path. u. Pharmacol., 1885, Band xix.

[6] Zeit. f. klin. Med., Band xii, xv, xvi.

[7] Virchow's Arch., 1878, lxxi.

[8] C. R. Acad. des Sci., Dec. 1, 1902, p. 928.

[9] Amer. Med., 1904, vol. viii.

[10] Virchow's Arch., Band xxx, p. 534.

[1] Untersuchungen uber die lungenentzundung.

With regard to the occurrence of pulmonary edema in man, two distinct groups of cases must be recognized. In the first of these the pulmonary lesion constitutes a part of a progressing dropsy, possesses nothing distinctive, and is apparently a factor of general edema. This type is seen in the terminal stages of cardiac dropsy and in the serous accumulations of chronic renal disease, particularly of the so-called parenchymatous type, whether acute or chronic. Subacute or chronic pulmonary edema may be a manifestation of various cachexias and especially of the secondary anemias due to cancer, chronic infections (tuberculosis), and other conditions in which profound anemia and varying degrees of dropsy constitute parts of the terminal stage. The edemas sometimes accompanying pernicious anemia and leukemia, and very commonly Hodgkin's disease, properly belong with this group. The multiplicity of affections with which pulmonary edema may be associated is well shown by the analysis of the 405 cases included in this report. There was a coexisting congestion of the lung in 235, tuberculosis in 69, croupous pneumonia in 38, atelectasis in 12, infarction in 12, gangrene in 5, bronchiectasis in 3; chronic pleurisy in 120, acute pleurisy in 23, and hydrothorax in 34. Bronchitis could be recognized in only 12 cases. In 350 of the cases associated cardiac lesions were also present; hypertrophy in 108, dilatation in 62, chronic endocarditis in 96, acute endocarditis in 7, myocarditis in 76, and in 1 the heart was malformed. In 35 cases there was a pericarditis, and in 6 a hydropericardium. In 140 of the cases arteriosclerosis was sufficiently marked to attract attention.

Renal lesions were present in 333 cases; chronic parenchymatous nephritis in 156, chronic interstitial nephritis in 126, acute diffuse nephritis in 42, and in 9 nephritis was observed, although the form is not stated in the notes. Hydronephrosis was found in 7 additional cases. The liver was congested in 150 cases and cirrhotic in 40. Although intracranial lesions are often named as important causes of pulmonary edema the cases herein studied offer no convincing evidence of an intimate association between the pulmonary lesion and meningeal or cerebral disturbances. In 29 cases there was a cerebral edema apparently due to the same causes as the pulmonary lesion. Meningitis was also present in 20 cases and in most of these evidences of sepsis are recorded. Cerebral hemorrhage was found in 7 cases and meningeal hemorrhage in 6. In 50 patients colitis, either dysenteric or probably uremic, was also observed. Ascites was a complication in but 25. With regard to the sex, 261 were males and 139 females; in 5 the sex is not stated. During an analysis of these cases one is struck by the fact that a large percentage indicates the presence of a frankly expressed or latent infection. I had hoped that the group would include a sufficient number to disclose something more constant and suggestive as to the etiology of the condition, but on the whole the result, in this respect, is disappointing. They all represent chronic, subacute or agonal edemas, but clearly indicate the character of the lesions with which pulmonary inundation may be expected to occur. In nearly 90 per cent. of the cases cardiovascular or renal lesions are present.

A most important and often unrecognized form of pulmonary edema, to which I wish especially to draw attention, is an acute, often fulminating affection, unaccompanied by other manifestations of dropsy, and often rapidly fatal. These are the cases that require prompt diagnosis and resourceful treatment. Clearly the cases are clinically different from the chronic, latent, and agonal edemas, and it is probable that their etiology and pathology are not essentially the same as those of the pulmonary edema which constitutes part of a general dropsy.

The condition at present under consideration is probably identical with, or closely related to, what Edye[1] calls paroxysmal edema of the lung, and what Müller[2] terms paroxysmal angioneurotic edema of the lung, and, in some respects, strongly resembles what Levi and Hanot[3] describe as edematous congestion. Steven[4] calls the

[1] Inaug. Diss., Zurich 1889.

[2] Correspbl. f. Schweizer Aerzte, 1891

[3] Arch. de Med., 1895

[4] Lancet, Jan. 11, 1902

affection acute suffocative pulmonary edema. Such acute or subacute forms possess clinical resemblances to some of the experimental types of pulmonary edema and are especially frequent in chronic interstitial nephritis, often when the latter is latent. Brouardel[1] regards the condition as inseparably connected with renal sclerosis, and almost invariably associated with aortitis. In the presence of renal or aortic lesions, exposure to cold, intense nervous stress, excitement, and the intemperate use of alcohol are important disposing factors. Huchard[2] was first to call attention to the frequency with which this type of edema complicates aortitis. Allbutt[3] believes that this form of pulmonary edema often accompanies aortic disease, and especially when the latter is associated with general arteriosclerosis—a point upon which Huchard lays no particular stress. Neither Huchard, Brouardel, nor any other observer with whose writings I am familiar, has recorded an acute pulmonary edema in the subjects of chronic parenchymatous nephritis. The affection is frequently a manifestation of latent arteriosclerosis and it is in just such cases that the inexperienced or careless physician is likely to make a diagnosis of asthma without discerning the relation between the pulmonary and the renal lesions.

The belief of Brouardel that pulmonary edema is always an indication of renal sclerosis is not supported by the observations of Humphreys[4] nor of Renaut,[5] both of whom have recorded cases in which there was no renal lesion. Landouzy[6] reported two cases with a history of polyarticular rheumatism and cardiovascular disease, the urine before, during, and after the attack having yielded no evidence of any renal disturbance. Huchard[7] recorded a case of gouty subacute aortitis with angina and many attacks of violent dyspnea due to pulmonary edema and associated with an abundant serosanguinolent sputum. It will be interesting to surgeons to note that this condition has been observed after anesthesia, particularly by ether. Poppert[1] ascribes it to the irritant action of ether, to which he also attributes postanesthetic bronchitis and bronchopneumonia. It is important, however, to notice also that many of these patients are septic and that, therefore, the bacterial origin of these complications cannot be ignored; it may be that the irritant action of the anesthetic favors pulmonary concentration or accumulation of bacteria or intensifies their local toxic action.

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[1] Bull. de l'Acad. de Med., 3me S. 1897, t. xxxvii, p. 500.

[2] C. R. Soc. de Med. des Hop., 1890: Bull. de l'acad. de Med., 3me S. 1897, t. xxxvii, p. 492.

[3] Lancet, July 8, 1903, p. 141.

[4] Brit. Med. Jour., July 10, 1886, p. 65.

[5] Bull. de l'Acad. de Med., 3me S. 1897, t. xxxvii, p. 557.

[6] Ibid., p. 562.

[7] Union Medicale, 1879.

Legendre[2] was the first to call attention to this affection in scarlet fever. Bernheim[3] and Rosenstein[4] believe that uremic asthma is due to an edematous swelling of the bronchial mucosa, a view with which Hertz[5] agrees. Lasègue[6] described an albuminuric bronchitis possessing some of the features of pulmonary edema. Le Breton[7] recognizes a form of acute pulmonary edema complicating rheumatism.

Jaccoud[8] described its occurrence in typhoid in which condition it has been observed also by Merklen.[9] The last named writer also recognizes pneumonia, grippe, rheumatism, and the intoxications especially alcoholism, as causes. Souin de la Saviniere[10] described it in scarlet fever, measles, pneumonia and bronchitis, and attributed some forms to emotional disturbances. Lemoine[11] during an epidemic of la grippe observed eighteen cases of what he called suffocating catarrh; the symptoms were highly suggestive of pulmonary edema.

Glasgow[12] has fully established the grippal origin of the affection, and recognizes that in many cases the infiltration is cellular. Teissier[1] believes that acute pulmonary edema results from the concurrent influence of infection, intoxication, nervous intervention, and mechanical disturbance of the circulation. Eichhorst[2] notes the association of pulmonary with angioneurotic edema of the skin, and suggests that, in the lung, it depends upon some disturbance in the innervation of the pulmonary vessels. German pathologists and clinicians hold most strongly to the mechanical theory, and the French to the toxic. It is conceded by practically all observers that phenomena indicative of myocardial degeneration favor the occurrence of pulmonary edema.

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[1] Deut. med. Woch., 1894, No. 37.

[2] De l'oedema aigu du tissue cellulaire du poumon qui sue de la scarlatine, 1846.

[3] Lecons de clinique med. de Nancy, 1877.

[4] Pathol. u. Therapie d. Nierenkrankheiten, 2 Aufl. p. 196.

[5] Ziemssen's Cyclopedia of the Practice of Medicine, English translation, vol. v, p. 271.

[6] Arch. gen. de Med., 1879.

[7] These de Paris, 1884.

[8] Cliniques de la Pitie, vol. i, p. 567.

[9] La Med. Moderne, May 13, 1903, p. 145.

[10] Contribution a l'etude de la cedema aigu du poumon, These de Paris, 1873.

[11] Soc. Med. des Hop., March 5, 1905; La Presse Med., March 8, 1905, p. 151.

[12] Amer. Journ. of Med. Sci., April 1895, p. 425.

Noting the varied conditions under which this affection occurs one gropes in vain for a satisfactory demonstration of a single etiologic factor common to them all. In 1878 Welch, on the basis of experimental study, promulgated the theory that general pulmonary edema results from any condition which causes the blood, advanced in a definite period of time, to be greater from the right heart than from the left ventricle. No matter how this condition may be brought about it becomes evident that as soon as the progression of blood from the left heart falls short of that thrown into the pulmonary arteries there must necessarily be an accumulation in the pulmonary circulation and heightened blood content in the capillaries of the lung. Largely as a result of misapprehension and failure properly to construe Welch's statements, Sahli,[3] Grossmann,[4] and Loewit[5] have advocated theories which, when properly analyzed, in a general way are supported by data that sustain the theory advanced by Welch. Recent studies on the pathology of edema are not strongly in accord with the view that, as a rule, heightened intravascular tension is as important in the production of the affection as are bacteria and other toxic agents. The admitted toxic origin of many cases, the association of the process with recognized infections such as typhoid, pneumonia, scarlatina, and influenza, and the fact that bacteria are frequently demonstrable in the affected organs speak eloquently for a toxic or infectious element as influential in the production of the disease. Blumer[1] has shown that edematous lungs may contain a number of bacteria, among which may be mentioned pyogenic cocci, including streptococci, and also colon bacilli. The facts that pulmonary edema may run its course, from inception to fatal termination, in less than three hours, that the so-called spontaneous affection is closely mimicked by the adrenalin forms, and that clinically the arterial tension is commonly greatly elevated, are all strongly suggestive of a mechanical influence.

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[1] XIIIe Congres internat. de Med., 1900.

[2] Text-book of the Practice of Medicine, American translation, 1901, vol. i, p. 123.

[3] Arch. f. exper. Path., Band xix, p. 434.

[4] Zeit. f. klin. Med., Band xii, xv, xvi.

[5] Centralbl f. allg. Path. u. path. Anat., 1895; references to previous articles.

Bouveret[2] looks upon the condition as a sort of vasomotor storm, and Huchard has shown that the more violent the attack the more marked the rise in arterial tension in the earlier stages, and the more sudden and extreme the later fall. Morely[3] explains the frequent association of aortitis and pulmonary edema by the assumption that the inflammation within the artery is propagated to the contiguous nerves which reflexly dilate the vessels of the pulmonary system, in which the tension rises and is followed by serous transudation.

The albuminous expectoration following thoracentesis[4] and less commonly abdominal tapping for ascites[5] is usually attributed to the intense congestion following the altered pressure resulting from removal of fluid from the pleura or abdomen. Calvert[6] reports a case of acute edema of the lung occurring above a diminishing pleural effusion. Leopold-Levi[7] reported an instance of acute pulmonary edema in hysteria.

The morbid anatomy of pulmonary edema has been especially

[1] Albany Med. Annals, Aug., 1901.

[2] Revue de Med., 1890, vol. x, p. 241.

[3] Gaz. des Hop., Oct. 2, 1897, p. 1101.

[4] Riesman, Amer. Journ. of Med. Sci., April, 1902.

[5] Jougla, Revue Med. de Toulouse, 1879.

[6] Trans. Clin. Soc. of London, 1893, vol. xxvi, p. 43.

[7] Arch. gen. de Med., Oct., 1895.

studied by Rokitansky, Welch, Honnorat,[1] Renaut,[2] Cohnheim, and others.

On opening the chest the lung retracts slowly and, in some cases, shows almost no tendency to recede from the thoracic wall. In marked cases the affected area is rib-marked. The color of the organ varies with the amount of blood that it contains; rarely the lung is dark, almost purplish, and in such instances the discoloration is most marked posteriorly and at the base. In uncomplicated cases the pleura contains no noteworthy excess of fluid; on incising the pulmonary pedicle the bronchus is found to contain a reddish fluid which, in some cases, is rather viscid although this must be regarded as exceptional. A similar rose-tinted froth may escape from the mouth and nose. The lung is at once noticed to be heavier than normal and pits on pressure. Careful palpation usually reveals a somewhat obscured crepitation which is practically never uniformly distributed, and in the most dependent portions of the organ may be absent; it is everywhere less manifest than normal and leaves the impression that the crepitation is farther from the palpating finger than is usual. In some cases the lung is of a steel-gray hue and, on exposure to air, takes on a reddish tinge. The density of the organ varies with the degree of the edema and the extent of the solidification. Some parts of the lung, rarely large areas, may be gelatinoid, and in such cases there is evidently present a substance that partly congeals although most careful examination usually fails to disclose any abundance of fibrin; as a rule this substance is absent. The organ is usually more readily incised than normal and the denser the edema the less the resistance to incision. As soon as the knife passes the pleura the escape of of fluid becomes evident and as the incision extends frothy serum streams from the angle and sides of the cut. Slight pressure increases the flow, and, although at first almost clear, or but lightly colored, it rapidly becomes blood-tinged, and, when associated congestion is marked, may be deeply stained. In one instance I readily expressed 185 c c. of fluid, the specific gravity of which was 1.035. In many cases areas can be found in which the escaping fluid is not frothy, and if such parts be carefully excised and thrown into water they promptly sink. That the exclusion of air is not due to collapse is shown by the absence of depression and by the microscopic findings. Areas of hemorrhage and clearly defined infarcts are occasionally present but can hardly be regarded as a part of the process. The bronchial contents are usually frothy and colored by the presence of red blood cells; commonly the tint is pinkish or rose-colored, but may be sufficiently dark to suggest hemorrhage; when deeply stained it is sometimes purplish but reddens on exposure to the air. The peribronchial lymph nodes are usually abnormally succulent, and when excised fluid may stream from the cut surfaces; such fluid is practically always clear or slightly turbid; I have not seen it colored. The lung stem is frequently manifestly edematous. The bloodvessels are not constantly intensely engorged, although commonly coagula may be withdrawn from the pulmonary arteries and veins.

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[1] These de Lyon, 1887.

[2] Gaz. des Hop., April 20, 1887, p. 552; Bull. de l'Acad. de Med., 3me S. 1807, vol xxvii p. 557.

For microscopic study rapid and powerful fixing agents are necessary, and the portions of lung selected must be quickly excised by a knife possessing an extremely sharp cutting edge. The requisite rapid fixation may be secured by immersion in boiling water, boiling alcohol, absolute alcohol, or formalin, but the best pictures will be obtained from specimens fixed in saturated alcoholic solution of corrosive sublimate, Heidenhain's solution, or Zenker's mixture. Formol-Müller may be used, and for some purposes, osmium fixation is of value, but these fixatives are inferior to the solutions above mentioned and less valuable than the mixtures of Petrunkevitch and Bensley. Almost any stain will reveal the grosser lesions but for the demonstration of the finer cellular detail and the abundant proteid deposit, the aniline dyes are especially to be commended. The most careful students of the morbid histology of pulmonary edema have recorded dissimilar appearances. Welch speaks of the capillaries as distended with red cells, and Renaut finds the same vessels flattened and rendered impermeable by the compression of the exudate. In most of the lungs that I have examined the capillaries usually show no conspicuous overdistention and are frequently empty. Sometimes the absence of red cells is conspicuous, although in the more dependent portions of the organ more or less capillary distention is usually present. The most striking feature of properly prepared sections is the widespread inundation of all the pulmonary structures by an albuminous fluid, which in fixed preparations yields a finely granular deposit in the distended vesicles and interstitial structures. Dissociation of the septa is often conspicuous. In some cases the interstitial swelling is especially marked in the submucosa of the smaller bronchi and bronchioles, the lumina of which are clearly encroached upon by the swollen wall. The elastica is often stretched and fails to stain with its wonted intensity. The subserous and interstitial lymph vessels are frequently manifestly distended. All the more recent observers have shown that Legendre erred in the supposition that the edema was exclusively interstitial. The extent of the intravesicular accumulation varies. In some areas the vesicles and bronchioles are fully occupied by the fluid and cells; in most sections, however, vesicles or even lobules may be found in which the intravesicular fluid accumulation is slight. It would be an interesting but probably unprofitable speculation to discuss the method by which the fluid gains ingress into the air vesicles. It is probably poured directly through the alveolar wall, although upon this point we possess no accurate information. With regard to the cells present in the fluid I had hoped, in the earlier studies, to find these fairly constant in character and number.

An extended examination of sections shows that the cell-content, both intra-alveolar and interstitial, is not always qualitatively or quantitatively the same. In some cases the erythrocytes are numerous, in others they are scanty and often shadowy. This accounts for the difference in the color of the frothy mucus extruded from the air passages. In a few cases polymorphonuclear leukocytes are abundant, and in such instances, bacteria, positively chemotactic for these cells, can usually be demonstrated. Other examples of the affection contain fewer of the polymorphonuclear type and more mononuclear cells, especially the larger forms. Detached vesicular epithelium is always demonstrable; in some cases large cells, apparently of this origin, are sufficiently abundant to suggest active desquamation. Large vesicular cells similar to those described by Pratt[1] as present in croupous pneumonia, are abundant, but I cannot speak with certainty as to their origin. They are frequently actively phagocytic. Fibrin is often found in marked cases but never in any quantity, even when gross specimens seem to indicate congelation of part of the contained fluid, careful staining failed to disclose any noteworthy quantity of fibrin; only here and there a few straggling fragments of the substance could be demonstrated. In some cases the larger bronchi are affected, and in one marked instance the tracheal mucosa manifested evidence of edema. The lymph-nodes at the hilum of the lung and along the bronchi frequently indicate the changes of an intense edema.

It will be observed that the abnormal fluid is too richly cellular to be regarded as simply a transudate, and, on the other hand, rarely contains a sufficient number of leukocytes to constitute a frank exudate. As Cohnheim and others have noted, the highly albuminous nature of the fluid is against the assumption that it was purely a transudate—a view also inconsistent with its richness in cells. Renaut compared it with the serocellular exudate observed in urticaria, but probably errs in the supposition that its character justifies a belief in its vasomotor origin. Rowland's[2] inclination to call it an acute inflammatory edema seems, on anatomic grounds, to be well taken. Dieulafoy[3] believes that cases occur in which the edema is largely bronchial, and others in which the bronchi and vesicular structures are both involved, and to these instances he gives the name bronchopulmonary edema. The condition has been described as an epiphenomenon of chronic bronchitis, but when we recall that bronchial irritation is a frequent complication of chronic renal and cardiac disease the connection seems less intimate than it would otherwise appear.

The symptoms of acute pulmonary edema are characterized by suddenness of onset rapid progress with an early fatal termination or relatively quick subsidence. Death may occur during the first attack or may terminate a recurrence. Repeated attacks are not uncommon; Merklen[1] observed three seizures in the same individual, and Lissaman[2] records a case in which seventy-two attacks occurred in two and a half years; there were twenty attacks in twelve months and a maximum of thirty-five in three months. Hewlett[3] observed five attacks in one patient; all followed coitus. Another patient had four attacks, and still another ten. Poulain[4] and Potain[5] were aware of the tendency to recurrences. All of Hewlett's patients were women, but a general survey of the literature does not indicate that sex is an important factor. Dieulafoy[6] was fortunate enough to observe a patient from the inception of the disease to recovery; the first symptom occurred during a physical examination, thereby enabling him to follow the signs closely. As most of the attacks occur at night complete observation is rarely possible. There is usually a rapidly developed sense of oppression, something resembling air hunger, or a feeling that the ventilation of the compartment is unsatisfactory. The patient seeks an open window; the respirations may be at first, or for a very brief period, deepened and prolonged, but quickly become shorter and more shallow, the sense of suffocation progresses, the face takes on a pinkish, then livid, and finally an intensely cyanotic hue, the hands and feet become cold and frequently a cold perspiration appears. The sweating is rarely intense and is often absent. A few observers have noted the occurrence of intense pain in the chest; in Lissaman's patient the pain was agonizing. The rapidity of onset and intensity of the respiratory phenomena have led to the name acute fulminating pulmonary edema, and so rapid may be the progress of the affection that in fifteen or twenty minutes after its inception death may appear impending. In typical cases a conspicuous symptom is the appearance of a pinkish, salmon-colored or more intensely red expectoration, which led Huchard to use the name hemoedema. The frothy fluid seems to be ejected from the respiratory passages and distinct cough with expectoration, as ordinarily observed, may be absent. The quantity of fluid coming from the air passages is sometimes enormous; Merklen says it may be two liters (approximately one-half gallon); Lissaman's patient ejected 1260 c.c. (42 ounces) in eight hours. Microscopically this fluid contains a variable number of red cells, although occasionally these elements are absent; in the earlier stages leukocytes and epithelium are not abundant and rarely in any stage are they numerous. Chemically the most striking feature is the high albumin content of the sputum.

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[1] Contributions to Science of Medicine by Pupils of William H. Welch, 1900, p. 265.

[2] Lancet, Jan. 25, 1902, p. 225.

[3] Clin. Med. de l'Hotel-Dieu de Paris, 1898, vol. i, p. 23

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[1] La Med. Mod., May 13, 1903, p. 145.

[2] Lancet, Feb. 8, 1902.

[3] Intercolonial Med. Journ., Dec. 22, 1903, p. 611.

[4] La Presse Med., Dec. 24, 1898.

[5] La Sem. Med., 1898.

[6] Bull. de l'Acad de Med., 3me S. 1897, tome xxxvii, p. 512.

In one of Hewlett's cases analysis showed 7.5 per cent. of albuminous bodies; the salts were 0.728 per cent., that is about the same as in the blood. Mucin was absent. In rare cases no expectoration occurs. Dieulafoy states that the absence of expectoration is indicative of a severe attack.

Among the conspicuous symptoms of this disease are those referable to the cardiovascular system. Huchard believes that the more intense the vascular phenomena the worse the prognosis. In severe attacks the initial rise in arterial tension is striking; the average blood pressure in three of Hewlett's cases was 213 mm. The elevated pressure is rarely maintained and in severe cases the fall may be more rapid than the rise; Morely observes that this may be taken as an evidence of cardiac fatigue. The cardiac pulsations at first are bounding, then the full elevated pulse rapidly becomes weaker with progressing ventricular exhaustion. At the inception of the attack the violent beating of the apex and accentuation of the second sound may be most conspicuous; as the affection progresses, the force diminishes, the apex impulse becomes less evident, and in severe cases may be imperceptible. The high tension pulse becomes more rapid and weaker, eventually thready and finally almost if not quite imperceptible. In the case reported by Crummer[1] there was a typical Corrigan pulse. The previously intense dyspnea grows more marked, cyanosis deepens, and brief intervals of unconsciousness appear. A rapidly developed delirium, and also convulsions, may occur. The average duration of the attack is from three to four hours, although death may occur in twenty minutes, or recovery, by a more gradual subsidence of symptoms, may prolong the paroxysm to twenty-four hours, rarely longer. Throughout the attack the temperature manifests no especially noteworthy character; it is usually normal, although Morely has seen it attain 104° F. Probably it is influenced more by antecedent or concurrent conditions than by the edema itself, and hence when the attack is superimposed on influenza, rheumatism, or typhoid the temperature phenomena may be regarded as manifestations of the associated affection rather than a part of the edema.

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[1] Northwestern Lancet, June 1, 1902, p. 203.

The physical signs of the condition may be regarded as its most constant feature. As the salmon-colored expectoration may be absent the diagnosis must be based upon the data obtained by percussion and auscultation. The usual physical signs of heightened arterial tension, discernible in the earlier stages of the attack, are rapidly lost, partly as a result of changes in tension and progressing myocardial weakness, but to a greater degree because of the progressing intensity of the pulmonary sounds. Of the latter the first to appear are fine crepitant rales which rapidly extend throughout the lung suggesting, as Morely observes, the rising tide of the sea.

Strumpell summarizes the respiratory phenomena as hurried, labored, and rattling. Fine crepitant rales are obscured by the loud bronchial bubbling. A most striking feature of the affection is its influence on the percussion note; one would naturally expect the progressing inundation of air vesicles to be attended by lessened resonance, but as a matter of fact the reverse occurs, for which condition Huchard suggested the name paradoxic percussion. It is probable that this phenomenon is due to bronchoplegia and to overdistention of lobules with air. This change extends the margins of the lungs and reduces the area of precordial dulness.

During the rapid examination of a patient a number of possible diagnostic errors suggest themselves. Like pulmonary embolism the symptoms are evolved rapidly and are largely cardiac and pulmonary.

In embolism, however, the physical signs do not begin with the symptoms, the percussion note never rises, the lesion is circumscribed and the expectoration scanty and not albuminous. Often a source of the embolus can be found. Morely observes that acute asthma and acute pulmonary edema are often confused; in both, the symptoms develop and subside rapidly, repeated attacks are common and both are especially frequent at night; the two affections are characterized by intense dyspnea. In asthma[1] the pulse is less influenced; cyanosis is rarely marked, indeed an ashy pallor is common. The prodromal wheeziness and respiratory discomfort of an impending asthmatic attack are usually absent in acute pulmonary edema. Paradoxic percussion is rarely observed in asthma, and auscultation indicates an abnormal dryness of the bronchi rather than an excess of moisture. The asthmatic cough is unproductive and expectoration scanty. The evidences of a chronic bronchitis are usually present, the respirations are not notably increased, inspiration is short, and expiration prolonged and difficult. The expectoration is pearly and viscid, frequently contains Curschmann's spirals and Charcot-Leyden crystals, and is never salmon-colored nor highly albuminous; red blood cells are absent. The chronic pulmonary edemas of cardiac and renal diseases develop slowly, show no paroxysmal characters, are at first local and manifestly influenced by gravity, and extend slowly; the associated cardiac and renal diseases are commonly manifest. The intense chest pain at first suggests pleurisy, but the dyspnea, salmon-colored expectoration, more deeply seated pain not possessing the features of the pleuritic stitch, the character and distribution of the rales, and the absence of friction sound render differentiation easy.

To be of any value the treatment of this condition must be prompt and energetic. Grossmann, noting its production by muscarine, suggested an antagonist to this substance and recommended the use of atropine, but those who have tried the remedy have found it disappointing; Huchard believes that atropine intensifies the bronchopulmonary paresis, impedes diuresis and is consequently not only unsafe, but dangerous. Teissier[1] suggests that amyl nitrite may be of value, but I know of no one who has tried it. Digitalis, or better digitalin, camphor in the form of comphorated oil, caffein, or hypodermics of ether may be tried. Flint[2] recommends hydragogue purgation, dry cups to the chest, and sinapisms; the hot air bath may be advised and oxygen sometimes affords marked relief. Huchard deprecates the use of vesicatories and other forms of counterirritation largely because of their depressing influence on the renal excretion. All authors who have tried the remedy commend bloodletting as the surest, safest and the most prompt measure for combating acute pulmonary edema. It removes toxic substances, lowers the venous tension, rapidly lessens the pressure on the right side of the heart, and therefore diminishes the cardiac embarrassment, antagonizes any tendency to pulmonary congestion and exerts a rubefacient influence on any exudate in the interstitial tissue of the lung. The quantity of blood withdrawn must be determined by the tension and the ability of the patient to withstand its loss; Huchard advises the extraction of 300 c.c. (10 ounces) to 400 c.c. (13 ounces). Tapping the right ventricle has been suggested. The earlier phlebotomy is practised the better the results. If not resorted to promptly the period in which the most striking and greatest benefit is to be expected rapidly passes. Wet and dry cups are less efficient than the free and more rapid withdrawal of blood from a vein. Caffeine, strychnine, musk, camphor, digitalis, ether, and alcohol are useful to supplement the good effects of bleeding, but cannot in any way be regarded as substitutes. Bouveret[3] in addition to bleeding recommends large doses of alcohol, the subcutaneous use of ether and caffein, and drastic purgation.

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[1] See also von Rieckhoff, Inaug. Diss., Munchen, 1904. On the Relation of Asthma and Lung Edema

A knowledge that the attacks are likely to recur and may at any time prove fatal at once suggests the importance of precautionary measures advantageously based on the treatment of any predisposing or more active etiologic condition upon which they depend; especially is this true of cases in which the underlying condition is chronic cardiac or renal disease, or arteriosclerosis. Huchard lays particular stress on the constant supervision of the renal functions, and, on account of its great value in cardiovascular and renal diseases, strongly advises the use of a milk diet. The iodides which have been regarded as of especial value in arteriosclerosis should be used with caution. The patient must be guarded against cold, exposure, overexertion, and dietetic, alcoholic, and sexual intemperance. In these cases Brouardel[1] has called attention to possible medico-legal complications. Should a patient promptly succumb after any form of treatment, or after an alcoholic debauch, cold, or exposure, the suggestion of poison may be raised. For his own protection it is important that the attending physician, immediately upon recognition of the malady, should apprise the relatives and friends of the unfavorable prognosis and imminent danger of a sudden or at least rapid fatal termination. *March* 1, 1906.

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[1] La Presse Med., Aug. 11, 1900, p. 101.

[2] Treatise on the Principles and Practice of Medicine, 1873, fourth edition, p. 256.

[3] Revue de Med., 1890, vol. x, p. 241.

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[1] Discussion of Huchard's paper, Gaz. des Hop., April 29, 1897; also Bull. de l'Acad de Med., 3me S. 1897, vol. xxxviii, p. 509

Chemical and Microscopic Study of Urine during Life, Followed by Histologic Examination of the Kidneys of the Same Patients.

By JOHN FUNKE, M.D.

Having found casts and albumin in urine excreted by the kidneys of individuals who I was told presented no clinical evidence of a kidney lesion, I concluded to determine whether casts and albumin are not found in urine excreted by organs which present little or no evidence of nephritis at postmortem. Accordingly, I began the routine urinalysis of patients at the Philadelphia Hospital. At first I selected only such cases as were likely to come to autopsy soon, but upon careful consideration it occurred to me that perhaps such patients would not give the desired information, since decided changes might occur in the urine and the kidneys during the last few days of life. Cases were then selected indiscriminately and chances of their coming to autopsy assumed.

During the investigation the urine of 172 patients was examined. In 59 cases the urine was examined twice; in 91 it was examined once; in 16 three times; in 3 four times; in 3 five times; in all 284 examinations were made.

That albumin may be overlooked or be absent at one examination is illustrated by the analysis, which shows that in those cases where the urine of the same patients was examined five times, albumin was demonstrated three times out of the five examinations in one case and once out of the five times in two cases. Where the urine was examined four times albumin was found at each test in but one case; in one patient it was present once out of four tests and in another twice. Where the urine was examined three times in the same patient albumin was present at each test in seven cases, twice out of three tests in four cases, and once in three cases.

Of the one hundred and seventy-two patients examined sixteen came to autopsy.

Case I.—The urine was examined once, but contained neither albumin nor casts; urea, 2.3 per cent. Death occurred seventeen days after the examination. Both kidneys were about normal in size, the capsules were not firmly adherent; the cortices were pale but normal in width. Death was due to ileocolitis. Microscopically the epithelial cells of many tubules were degenerated, necrotic, and desquamated. The capsule was slightly thickened, but the interstitial tissue was not greatly increased. While the condition was not marked, yet the microscopic picture revealed changes like those found in chronic diffuse nephritis.

Case II.—The urine contained a trace of albumin; urea, 2.8 per cent; in the sediment were a few long hyaline casts. The patient died one and a half months after the urinalysis. The anatomic diagnosis was arteriosclerosis, cystitis, and chronic diffuse nephritis. The kidneys were smaller than normal; the capsule stripped off with some difficulty; the cortices were narrowed, especially near the poles. Microscopic section showed a thickened capsule, and an increase of the interstitial tissue of the cortex, particularly near the medulla. Many of the capsules of Bowman were thickened; in some of the tubules the epithelium was degenerated and necrotic; others contained hyaline plugs. From the microscopic changes observed these kidneys should be regarded as manifesting lesions of chronic diffuse nephritis.

Case III.—The urine was examined but once; it contained no albumin but a few long hyaline casts. Death resulted from tuberculosis of the lungs; the exact interval between the date of death and the urinalysis cannot be given as the date of the latter was not recorded; it was about three weeks. The kidneys were normal in size; the capsule was drawn into the parenchyma at points; the width of the cortices was not much altered, but they contained pale areas. Microscopically the sections showed no thickening of the capsule, but a slight increase of the interstitial tissue. The epithelium in many of the tubules was swollen, granular, and degenerated. The microscopic picture of these kidneys is clearly that of chronic diffuse nephritis.

Case IV.—At the first examination the urine showed a trace of albumin; urea, 1.4 per cent.; at the second examination the amount of albumin was greater; the urea, 0.9 per cent. The second urinalysis was done forty-two days after the first, and death occurred two months after the last examination. The cause of death was tuberculosis of the lungs. Both hyaline and granular casts were found at each examination. The kidneys were reduced in size; the capsules were thickened; the surfaces of the organs granular and the cortices were narrowed. The renal vessels were markedly sclerotic. Microscopic examination revealed an increase of fibrous tissue in the cortex and a thickening of the capsules. Scattered throughout the sections were islands of hyaline substance; the same substance was occasionally found in the tubules and in large cyst-like cavities, where it was often disposed in concentric layers. When the amount of material in the tubules was small the epithelial cells were fairly well preserved. With all the methods employed the material selected the same stain as the substance forming the framework of hyaline casts. In the medullary portion the interstitial tissue presented myomatous changes. The walls of the vessels were markedly thickened. Barring the myomatous changes and the presence of hyaline substance the picture is like that of chronic interstitial nephritis.

CASE V.—The urine showed albumin, 0.3 per cent.; urea, 3 per cent.; hyaline, granular, and epithelial casts. Death occurred seven days after the examination from tuberculosis of the lungs. The kidneys were red at points and yellowish red in other places; the cortices were pale but not much altered in width. The microscope showed degeneration and necrosis of the epithelium; the condition involved most of the tubules. There were many tubercles in the sections; giants cells were found in the interstitial tissue. Hyaline substance like that in the sections of the preceding case was found, occasionally in cysts.

CASE VI. The urine: albumin, none; urea, 1.5 per cent.; casts, none. There was but one examination; death occurred sixteen days after the urinalysis from tuberculosis of the lungs. The kidneys were normal in size but pale at some points; the cortices were about normal in width. The epithelium of many tubules was swollen and granular; the nuclei were either invisible or faintly visible; many were destroyed. The collecting tubules and the tufts were fairly well preserved. Diagnosis, chronic diffuse nephritis.

Case VII.—The urine: albumin, none; urea, 1.8 per cent.; casts, none. The patient died two months after the urinalysis; the postmortem diagnosis was aneurysm of the aorta and arteriosclerosis. The kidneys were smaller than normal; they were firm and the capsules adherent; the cortices were narrowed at places. The interstitial tissue was greatly increased; the capsules of Bowman were thickened and many tufts were hyaline. In many of the tubules the epithelium was degenerated and necrotic. These changes were more advanced in some sections than in others. Hyaline substance was found in some of the tubules where the epithelium was necrotic, but not in those where it was swollen. The walls of the vessels were thickened. This is a case of chronic interstitial nephritis of arteriosclerotic nature.

Case VIII.—The urine: albumin, 0.25 per cent.; casts, none. The sediment contained many polymorphonuclear leukocytes. The kidneys were large, pale; the capsules were not adherent; the cortices were wider than normal and showed grayish striations. In the pelves was considerable purulent substance. The patient died two weeks after the urinalysis. The epithelium of the tubules was swollen and necrotic; the medullary portion contained many polymorphonuclear leukocytes, and in some parts distinct abscesses. Death in this case was due to the septic condition incident to the suppurating cystitis, pyelitis, and nephritis.

Case IX.—The urine (first examination): albumin, 0.2 per cent.; casts, hyaline; (second examination) albumin, 0.2 per cent.; casts, none. The patient died three weeks after the urinalysis from cerebral softening, arteriosclerosis, and suppurating endometritis. The kidneys were reduced in size; the capsules were adherent and thickened; the cortex of the kidneys was narrower at points. The renal vessels were sclerotic. The interstitial tissue was increased; some of the Malpighian bodies were hyaline and the epithelial cells in many tubules were degenerated. Here the lesion was obviously chronic interstitial nephritis.

Case X.—The urine: albumin, trace; casts, none. The patient died two weeks after the urinalysis from carcinoma of the head of the pancreas, with involvement of the biliary passages and the liver.

The kidneys were nearly normal in size; the capsules were slightly adherent; the cortices showed no macroscopic alterations. Sections revealed an increase in the thickness of the capsule and advanced interstitial changes. The epithelium of many tubules was granular; the collecting tubules and the loops of Henle contained granular detritus. Diagnosis, chronic interstitial nephritis.

Case XI.—The urine was examined once early in the course of the disease; it showed no albumin nor casts; urea, 1.8 per cent. The patient died nineteen days after the urinalysis. At postmortem the ileum contained an ulcer possessing all the characters of the local lesion of typhoid fever; there was also gangrene of the gums and the upper lip, and catarrhal pneumonia. The bacillus typhosus was isolated from the spleen and the liver. The kidneys were large, deeply injected; the cortices were swollen and the cut surfaces dripped blood and presented red striations. The epithelium of the convoluted tubules was swollen and granular, the nuclei were scarcely visible; many of the tufts were engorged. I believe the acute nephritis in this case developed as a part of the typhoidal condition and after the urinalysis was performed.

Case XII.—The urine: albumin, trace; casts, none. The patient died four days after the examination of the urine; death was due to carcinoma of the stomach with metastasis to the liver. The kidneys were increased in size; they were reddish purple, and the cut surfaces dripped blood; the capsules were adherent. Sections revealed an increase of the interstitial tissue, thickened capsules, and some hyaline tufts. Some of the epithelium of the convoluted tubules was degenerated. Diagnosis: chronic interstitial nephritis and congestion of the kidneys.

Case XIII.—Two examinations were made in this case. Albumin, none; casts, none; urea: first examination, 1 per cent.; second examination, 2 per cent. The patient died two months after the last examination, from tuberculosis of the lungs. The kidneys were decreased in size; the capsules were adherent, the cortices were pale but not much altered in width. The microscope showed the most marked changes in the tubules, where the epithelial cells were necrotic and fragmented. These changes were more advanced and more extensive in some sections than in others. The interstitial tissue was increased, and it contained collections of lymphoid cells here and there. Some of the Malpighian tufts were hyaline and a few of the bloodvessels contained hyaline thrombi. The most conspicuous changes in these organs were tubular, which were of a chronic nature.

Case XIV.—Here two examinations were made: (1) albumin, decided trace; casts, hyaline and granular; (2) albumin, decided trace; urea, 1.8 per cent.; casts, hyaline and granular. The second examination was made one month after the first, and death occurred six days after the last urinalysis, from tuberculosis of the lungs and tuberculous ulceration of the intestine. The kidneys were large and pale; the cortices were pale, swollen, and presented grayish striations. The epithelial cells were swollen and granular; the nuclei were degenerated. Occasionally the swollen epithelial cells contained small hyaline bodies, some of which were smaller, others larger than red blood cells. When the cells disintegrated the bodies were free in the tubules. Many tubules contained compact hyaline substance. The interstitial tissue was markedly increased, and was abundantly infiltrated with mononuclear cells. Sections fixed in osmic acid showed no fat in the epithelial cells. While these organs at the time of the examination were large white kidneys, it is reasonable to assume that had the condition progressed for some time they would have eventually become the small white type, as indicated by the presence of the formative tissue.

Case XV.—The urine: albumin, 3 per cent.; casts, granular and hyaline; red blood cells, few. Death occurred three days after the examination, from carcinoma of the head of the pancreas, with metastasis to the liver and to the lungs. The kidneys were increased in size; they were bright red in color; the capsules were adherent and the cortices were swollen and dripped blood. The epithelial cells were swollen, granular, and desquamated; the vessels were engorged and the interstitial tissue was increased. Diagnosis: acute parenchymatous, superimposed upon a chronic interstitial nephritis.

Case XVI.—The urine: albumin, trace; casts, hyaline. The patient died two weeks after the urinalysis from carcinoma of the stomach with metastasis to the liver. The kidneys were normal in size; the capsules were slightly thickened and adherent; the cortices presented pale areas here and there. The epithelium was necrotic and desquamated; the interstitial tissue was increased, but not markedly. Diagnosis, chronic diffuse nephritis.

An analysis shows that in four cases the urine contained neither albumin nor casts, but the kidneys of these cases presented marked degeneration and desquamation of the epithelial cells of the tubules. The question at once arises, Did the changes found in these kidneys occur during the agonal period or was the urine examination insufficient to say positively that it was albumin-free at all times? In all but one of these cases the urine was examined once. Had the urinalysis been performed oftener perhaps the albumin would have been demonstrated. This view is supported by the fact that in those cases where the urine was examined, three, four, and five times, albumin was sometimes demonstrated, but sometimes it was absent. This argument is supported by the findings of Case III, where albumin was absent but casts were present and the kidneys showed a chronic diffuse nephritis.

These results seem to corroborate the findings of Cabot (*Journal of the American Medical Association*, March 18 and 25, 1905), but I am not willing to draw conclusions that urinary examinations are untrustworthy in the acute and chronic diffuse forms of nephritis, for I believe the number of cases is entirely too small, and the examination of urine not sufficiently thorough to justify it. I can scarcely believe that all the changes observed in the kidneys which secreted urine apparently free from albumin occurred during the agonal period, since the changes were sometimes as extensive as those seen in the kidneys which secreted albuminous urine.

In conclusion, I wish to express my thanks for the valuable assistance given me by Mr. Widdowson and Mr. Funk, research students of the Jefferson Medical College, and also my indebtedness to the internes, chiefs, and nurses of the Philadelphia Hospital who lent valuable aid. *November* 23, 1905.

Vincent's Angina: with Report of Cases.

By J. DOUGLAS BLACKWOOD, Jr., M.D.

In 1896, Vincent[1] described a spirillum and a fusiform bacillus occurring together in certain cases of angina of an ulcerative type. This was followed by reports of cases by Bernheim,[2] Mayer,[3] Royster,[4] Crandall,[5] A. Gross,[6] Toebben,[7] and many others.

Lesion. The lesion produced by the spirillum and fusiform bacillus is ulcerative in type in contradistinction to that produced by the diphtheria bacillus. When the necrosis is superficial, the necrosed epithelium, on the surface, often hides the depth of the lesion, thus resembling diphtheria very closely. If the layer is removed a distinct ulceration will be seen. While, as a rule, the deposit is easily removed, as reported by Mayer,[3] at times only the superficial layer is friable, according to Auché,[8] or the whole deposit may be hard to detach, as mentioned by H. W. Bruce.[9]

This deposit, however, is not due to the formation of a false membrane on the surface of the diseased area, but to necrosis of the superficial layers of that area with the formation of an ulcer.

The ulcer varies in depth and extent, having perpendicular edges which may or may not be injected and presents many granulations which bleed easily.

H. W. Bruce[9] divides the process into two types, namely: *Mild diphtheroid type,* which is generally unilateral, superficial, limited in extent, and gives no swelling or injection of the fauces, with slight glandular enlargement on the side of the lesion and slight elevation of temperature, lasting from twenty-four to forty-eight hours. There is no immediate change in the throat condition with the drop of temperature, but the slough finally drops off and an ulcer is revealed which quickly heals.

Ulceromembranous type, in which the condition spreads rapidly over a greater area and is much deeper. There is a slow separation of the slough in ten to fourteen days, during which time one-half of the tonsil or uvula may be destroyed, followed by granulations which bleed readily and heal rapidly. There may or may not be injection about the edges of the ulcer according to the severity of the case. There may or may not be fever, and albuminuria is rarely present. Glandular enlargement occurs, but never goes on to suppuration as it does in the adenitis following or occurring with the streptococcic angina of scarlatina.

This type may cause septic pneumonia and death, as in a case reported by H. W. Bruce.[9]

One attack does not confer immunity from subsequent attacks, as stated by Bruce[9] and shown by Case I in this report.

Mayer[3] states that endocarditis may also follow this disease.

The B. fusiformis averages from 6 to 12 microns in length, being thick in the central portion and thinning out at both ends. There are flagella attached, one to each end and two to the sides, giving the bacillus an eel-like motion in a hanging-drop preparation, which together with its reaction with Leishman's stain leads A. E. Wright[10] to think that this micro-organism is not of bacillary origin but has affinities with a trypanosome. It is stained by most of the common aniline dyes and often shows vacuoles and other forms of degeneration, but no spores are demonstrable. It does not grow readily upon ordinary culture media either under aërobic or anaërobic conditions except, according to G. Angelici,[11] when cocci are added. The same observer also states that acetic acid has a favorable influence and sugars inhibit its growth. These bacilli often occur in pairs and frequently in groups. Angelici also states that this bacillus is the same as the B. hostilis of Seitz, and can be found in morbid processes throughout the alimentary canal.

The Spirillum. This is a faintly staining, wavy, long, thin, delicate micro-organism which stains with ordinary aniline dyes, but does not stain by Gram's method. It is considered by many to be a normal inhabitant of the buccal cavity, only becoming pathogenic in the presence of other micro-organisms.

These micro-organisms may be found in pure culture in the diseased areas, especially in those of deep ulceration. When the ulceration is superficial there is often a polymicrobic infection, the spirilla and fusiform bacilli being associated with streptococci and staphylococci. While de Stoecklin[3] claims that the presence of these micro-organisms precludes the existence of B. diphtheriæ, Vincent, Toebben,[7] and Auché[8] have reported cases in which the three organisms were present and R. C. Rosenberger[12] has reported the organisms present in a case of noma.

Both of the organisms have been found by Grenet[13] in cases that gave no evidence of stomatitis.

The object of this paper is to report nine cases of this infection in children ranging from two to ten years which occurred in the Children's Department of the Philadelphia Hospital during the summer of 1904. One of the positive smears was made from the throat of an apparently healthy child who showed no signs of ulceration or disease of the throat, tonsils, tongue, cheeks, gums, or lips. In all, smears were examined from twenty-one children, and of these eight showed the presence of the fusiform bacillus in association with Vincent's spirillum, and one showed the presence of the fusiform bacillus alone. In one case pneumococci were found in the smears from the throat while the spirillum and fusiform bacillus were found in that from the gums. The other twelve smears were made from the throats of children in the same department, but showed no signs of either of the micro-organisms mentioned. For brevity we will dispense with detailed accounts of primary histories and physical examinations of the cases, only giving their initials and the symptoms which they exhibited during this infection.

CASE I.—J. W., female. During the course of the infection the patient had bronchopneumonia, so it is impossible to state to what extent her irregular temperature (which rose as high as 103.2° F.) was due to this infection. During the course of the pneumonia the patient had two attacks of Vincent's angina, the seat of the first attack being upon the upper lip and lasting three days, being described in the history as an exudate. The seat of the second attack, which was a true angina, was upon the tonsils and pharyngeal pillars, which were covered with yellowish ulcerated patches. The tonsils were swollen and injected. The patches disappeared first from the tonsils and then from the pillars. The tonsils then became reduced in size and the redness subsided. The attack lasted twenty-two days, and there was no glandular enlargement.

Case II.—J. D., male. This patient had a slight elevation of temperature. There were a few points of ulceration on the lips and bleeding from the gums. There was also a white superficial exudate on the tonsils. Examination of the smears from the tonsils showed the presence of pneumococci but no spirilla or fusiform bacilli, while that of the smears from the lips showed these microorganisms to be present. No glandular enlargement.

Case III.—H. A., male. In this case there was a sudden rise of temperature in the evening to 103.° F., followed the next morning by a drop to 101.2° F.; then rising in the afternoon to 103.2° F., and dropping the next morning to 99.4° F., and then rising to 101° F., followed by a gradual fall to normal. Smears from the throat showed the presence of Vincent's spirilla and the B. fusiformis. The postcervical glands were enlarged upon admission and showed no increase in size during the attack, which lasted four days.

Case IV.—A. W., female. There was a sudden rise of temperature to 102.3° F., followed by lysis lasting one week. During the first four days of the attack the child was slightly comatose, being aroused with difficulty, but during the remainder of the attack she became much brighter. The sites of the lesions were the side of the tongue, which presented a small patch, and the roof of the mouth, upon which were two smaller ones. During the first four days the tongue was heavily coated. At the end of four days the patches had entirely disappeared from the tongue and there remained only a slight reddening of the roof of the mouth. There was no increase of a previously existing glandular enlargement during the attack. Examination of smears from the tongue and roof of the mouth showed the presence of Vincent's spirilla and the B. fusiformis.

Case V.—M. A., female. Examinations of smears from the throat showed the presence of Vincent's spirilla and B. fusiformis. There was no rise of temperature.

Case VI.—J. E., male. Examination of smears was positive for spirilla of Vincent and B. fusiformis. No glandular enlargement. No fever.

CASE VII.—P. B., male. Irregular temperature, first rising to 100° F., then falling to 98.4° F., again rising to 101° F., followed by a drop to normal by lysis. No glandular enlargement. Smears from throat were positive for Vincent's spirilla and B. fusiformis. Attack lasted four days.

CASE VIII.—J. F., male. Healthy child. Smears from throat showed presence of B. fusiformis but no spirilla.

CASE IX.—P. H., male. Healthy child. Smears from throat showed presence of both Vincent's spirilla and B. fusiformis.

SUMMARY. Of these nine cases, seven were of the superficial or mild diphtheroid type of Bruce, and two were healthy children, smears from whose throats showed the presence of B. fusiformis and in one instance the association with the spirillum. The diphtheroid type of cases began with sudden rises of temperature, reaching as in Case III an elevation of 103° F. The temperature then pursued an irregular course, varying from 2° to 3° F. in its course or gradually dropped to normal, as in Case IV.

In all the cases showing fever the temperature fell by lysis. The pulse and respiration rate followed the temperature curve. As a rule, the patient did not show any marked constitutional effects except in Case IV, this patient being comatose for the first four days of the attack. The seat of the attack was on the lips, tongue, gums, cheeks, tonsils, or pharynx, and in none was there marked destruction of tissue. In none of the cases was there glandular enlargement except that which existed prior to the disease. In all cases the fusiform bacilli were in greater number than the spirilla, thus fulfilling the claims of Bruce.[9] The attack lasted from four days, as in Case III, to twenty-two days, as in Case I, the ulcerative condition still persisting after the temperature had become normal. My thanks are due to Dr. R. C. Rosenberger, Director of the Clinical Laboratory of the Philadelphia Hospital, for assistance on these cases and for guidance in my references.

January 25, 1906.

Bibliography.—1. Annales de l' Institut Pasteur, 1896, p. 488. 2. Deutsch. med. Woch., 1897. 3. Amer. Journ. Med. Sciences, Feb., 1902. 4. Arch. of Pediatrics, Aug., 1903. 5. Journ. Amer. Med. Assoc., July 23, 1904. 6. Post-Graduate, June 1904. 7. Berl. klin. Woch., May 23, 1904. 8. Lancet, March 15, 1904; Gaz. Hebdomadaire des Sci. Med., Bordeaux. 9. Lancet, July 16, 1904, p. 135. 10. Lancet, July 9, 1904. 11. Il Policlinico, Rome, Feb. 20, 1904. 12. Amer. Medicine, July 23, 1904, vol. viii, No. 4, p. 161–163. 13. La Presse Med., June 29, 1904, p. 41.

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Recent Studies in Measles.

BY RANDLE C. ROSENBERGER, M.D.

MANY observers by simply applying the blood, tears, mucus, from from the nostrils or bronchia to scarified areas, have tried to bring about the phenomena of measles, but without success.

The earliest authentic instances of inoculation experiments in measles were carried out by Home, of Edinburgh, in 1758 (quoted by Hektoen, cited below). He is said to have successfully inoculated measles from one person to another by scarifying the skin and applying upon this area the blood of a person suffering from measles.

According to Themmen the tears and blood from a case of the malady, placed upon the skin of five healthy children, produced no effect whatever.

In 1842 Katona (*Osterreich. med. Woch.*, 1843, No. 29) inoculated 1122 individuals with positive results in 93, and without any evil effects. He inoculated as in vaccination by means of a needle dipped into a fluid mixed with blood obtained by opening the small vessels when the eruption was at its highest. On the seventh day fever appeared with the usual early symptoms of the disease, followed by eruption on the ninth or tenth day, and in one instance not until the thirteenth day. (These inoculations were made during an epidemic, so that the opportunity for natural infection was present.)

Hektoen (*Journal of Infectious Diseases*, March, 1905) inoculated the blood from two cases of measles into healthy adults, following which there appeared in each instance a maculopapular eruption, rise of temperature and a branny desquamation of the skin. Though not definitely stating the nature of the virus, he claims that it is present in the blood of patients with typical measles during the first thirty hours of the eruption, and still retains its virulence for at least twenty-four hours, when such blood is inoculated into ascites broth and kept at 37° C. Speranza, Bufalini, Locatelli, Rossi, Figueri, Horst and Percival (quoted by Welch and Schamberg, *Acute Contagious Diseases*, 1905) all claim to have had successful results in the inoculation of measles.

Mayr (Hebra's *Diseases of the Skin*, 1866), Albers, and Thomson were unsuccessful in their attempts to produce the disease by inoculations.

As to the nature of the specific cause of measles there have been many attempts made to isolate it. Some observers have isolated a bacillus, others a coccus, while still others claim to have observed animal parasites. Since in other exanthemata, such as variola, vaccinia, and scarlet fever, suggestive bodies or parasites have been found, it seems possible that we may look to this group of organisms as causing or playing some part in the etiology of measles.

Doehle (*Centralbl. f. allgem. Path.*, 1892, iii, p. 150) noticed small oval bodies in the circulation and in the red cells, ranging from 0.5 to 1 micron in diameter.

Klein is quoted as having seen such bodies emigrate from the red cells and become actively motile just as if flagellated. In the red cell from which the body escaped there remained a vacuole corresponding in size to that of the emigrated body.

Zlatogoroff (*Roussky Vratch*, July 10, 1904) isolated from the blood in 17 out of 24 cases of measles a small bacillus, Gram positive, slightly motile, and usually occurring in pairs. Canon and Pielicke observed a bacillus in the blood, sputum, and secretions of the nose and eyes, which persisted throughout the disease, but disappeared when convalescence set in. It was isolated in 14 cases and grown successfully only in bouillon.

Borini (*Riforma Med.*, June 24, 1905) noted the presence of a bacillus in the blood in several instances during the malady, which developed in cultures after thirty-six hours. It was small and delicate, Gram negative, and died out after several transplantations.

Lesage (*Bull. de la Soc. des Hopitaux de Paris*, March 15 and 22, 1900) found a delicate micrococcus which grew best upon agar, stained faintly, and was Gram negative. It was found constantly in measles and was not present in scarlet fever nor in a number of healthy children. In 53 children who had the disease (measles) it was found twice.

Von Niessen (*Arch. f. Derm. u. Syph.*, 1902, vol. ix.) discovered in the blood and exanthem a bacillus which resembled the one studied by Canon and Pielicke but differed from this organism by growing upon glycerin agar and potato with a pinkish color. It was called the bacillus roseus.

Czajkowski (*Centralbl. f. Bakt. u. Parasit.*, 1895, Nos. 17 and 18) observed a bacillus in the blood, while Josias (*La Méd. Moderne de Paris*, June 2, 1902) failed to corroborate these findings in 2 per cent. of cases.

Arsamakor (*Revue de Méd.*, 1899, vol. xix.) in the examination of 305 cases of measles found a club-shaped bacillus five to six microns in length.

In the writer's observations studies were made of the serum obtained by blistering over the eruption in the early days of the disease. The vesication was accomplished by placing a small quantity of 20 per cent. ammonia upon absorbent cotton and covering with a sterile gauze dressing. The chemical was allowed to remain from twenty minutes to one hour. The serum was collected in sterile capillary glass tube and examined in the fresh state. Only upon the rarest occasions were red cells or leukocytes in any number observed in this fluid.

Upon examination with the oil immersion lens a more or less constant hyaline body was detected, possessing the following characteristics: In size it varied from one-tenth to one-sixth the diameter of a red blood cell. It was generally spheroid, while ovoid or pyriform varieties were present. It was, as stated, perfectly hyaline, and possessed or had attached to it a round or irregularly oval-shaped granule of a brownish-black color which was actively motile. This granule travelled around the entire periphery of the body in a most deliberate manner, stopping every now and then, and appeared to try to gain an entrance into the body. Where this phenomenon was noticed the pyriform shape was best brought out. In two or three instances flagella were seen; never more than two. In the same specimen of fluid another hyaline body, also motile but containing from two to four small motile granules, was occasionally seen. The first-described hyaline body, with the peculiar granule, was observed in thirty-nine out of forty-one cases of measles examined usually upon the second day of the disease. In the two unsuccessful instances the serum was not obtained until the fifth day of the eruption, when it was fading.

The body was stained with Wright's blood-stain, though poorly, and in these preparations the granule was seen to be situated eccentrically or upon the periphery. A few attempts have been made to cultivate the body in the small quantity of serum left in the tube, and incubated at 37° C., but without success. No bacteria were ever encountered in any preparation.

Though the nature of this cell is problematical it seems that it possesses characteristics constant enough to be classed amongst the cytoryctes. I do not presume or claim that this body is the cause of measles or that it plays any part in the etiology, yet its almost constant presence in the serum of the early eruption is a most interesting fact and seems suggestive.

No similar bodies were identified in normal serum, the serum from a few cases of scarlet fever, or the serum from a number of syphilitics. A very minute hyaline body was observed by the writer a couple of years ago in the serum from the vesicles in several cases of variola. The body was exceedingly refractile, very minute; possessed a rapid darting motion, and lacked the brownish-black granule.

I wish to extend my thanks to Dr. John D. Wilson for assistance in the work. *March* 1, 1906.

Iodophilia: A Pathological and Clinical Study of the Iodine Reaction in One Hundred Cases.

By JOHN C. DA COSTA, JR., M.D.

(From the Laboratory of Clinical Medicine and Therapeutics of the Jefferson Medical College Hospital).

Preliminary Considerations. If a dry specimen of normal blood be treated with a weak solution of iodine, the stroma of the erythrocytes and the protoplasm of the leukocytes stain a pale lemon-yellow tint, and the nuclei of the latter cells remain practically colorless, or, at the most, show delicate refractile points and shadows corresponding to the twists and the knots of the chromatin network. In numerous pathological conditions, however, the protoplasm of the leukocytes, especially those of the neutrophile type, when exposed to iodine, exhibits a peculiar susceptibility to the action of the metal, and stains a variable shade of brown. Such cells are known as iodophiles, and the reaction as iodophilia.

In addition to the iodine-stained cells one frequently finds, in normal blood, small numbers of irregularly-shaped plasma masses which react to the reagent and stain a deep mahogany color. These extracellular masses may be either free in the plasma, or, as is more often the case, incorporated with bits of cytoplasm derived from leukocytes which have been traumatically fragmented or disintegrated. No definite significance can be attributed to this form of extracellular iodophilia; it may be wholly wanting in blood teeming with intracellular iodophiles. In cases in which both the intracellular and the extracellular reactions develop—a finding occasionally observed—it is possible that the latter may be taken as a sort of index to the vulnerability of the leukocytes. There is also good reason to believe that some of these free iodine-stained masses are the remnants of blood plaques, while still others are plainly artefacts. It will be noted that the foregoing descriptions apply solely to the dried blood specimen, a point which must be emphasized, in view of the fact that fresh moist film of perfectly normal blood, exposed to iodine vapor before it has had time to dry, shows a precisely similar change. This, as Wolff has pointed out, means that the iodophilous substance, presumably glycogen, is normally present in the circulating leukocytes, although, as I shall attempt to explain subsequently, it is not demonstrable in the dried film prepared in the ordinary manner, owing to its excessive solubility. The presence of iodophilia in the *dried film*, then, is pathological, for in the normal dried specimen the reaction is consistently negative. Unless otherwise stated, the reactions detailed in this report invariably relate to dried spreads and not to the so-called "vital iodine-fixation" technique.

NATURE OF THE REACTION. Ehrlich's original opinion that the iodine reaction betrays the presence of cellular glycogen, is generally credited at the present time, though in the past this has been disputed by several investigators, notably by Czerny who maintains that the material responds to tests for amyloid, as a form of which he regards it. Goldberger and Weiss believe that peptone is responsible for the change. Personally, I have never been able to find the slightest trace of the amyloid blue in specimens treated with iodine and sulphuric acid, nor to develop a pink or rose color in films fixed in absolute alcohol, stained with methyl-violet, and decolorized with dilute acetic acid. This, however, may mean nothing, for technical methods suitable for microchemical differentiation in tissue may prove quite inadequate for blood work.

The facts that the substance stains mahogany-brown with iodine, that it exists normally in the leukocytes, and that it is highly soluble are, to say the least, strongly suggestive of its identity with glycogen.

To explain the *pathogenesis* of iodophilia there are two equally plausible theories, of somewhat different mechanism, but similar in that each admits that glycogen is a normal constituent of the leukocytes and in that each presupposes that some toxic principle must, so to speak, first cripple the cells before their glycogen content can be demonstrated. Thus, according to one theory (proposed by Wolff), iodophilia means that the cell-glycogen, normally so soluble in water that it is not affected by ordinary staining methods, has become, through a toxic influence, abnormally insoluble, and in consequence exhibits its affinity for iodine, being colored distinctively by this metal even in the dried blood film. According to another theory (fathered by Sorochowitsch), the reaction depends upon an interference, toxically bred, with the activity of a normal ferment which in conditions of health rapidly and effectually transforms the cells' free glycogen into glycose for combustion into excretory end products. Owing to this defect in catabolism glycogen accumulates within the leukocytes in sufficient excess to be recognized microchemically.

To the clinical inquirer it is perhaps immaterial which of these interesting hypotheses be accepted. The fact remains that iodophilia may rationally be interpreted as a sign of leukocyte degeneration caused primarily by a toxemia which renders the glycogen component of the cells abnormally susceptible to the selective action of iodine.

Present Status of Iodophilia. The iodine reaction has been a matter of more or less current medical interest since 1883, when Ehrlich described it, especially in relation to pus cells.

No one, however, seems to have taken up the test from a clinical standpoint until 1891, the date of Gabritschewsky's careful studies of its occurrence in diabetes mellitus and in leukemia.

Within the next ten years or so some half-dozen important contributions on the subject were published by European workers, prominent among whom may be mentioned Goldberger, Weiss, Livierato, Czerny, Kaminer, and Hofbauer. The activity of these investigators produced a mass of data, which though on the whole consistent, was in some details so conflicting that prudent clinicians hesitated to place dependence upon the test. It was this general lack of confidence that for several years made the term iodophilia synonymous with an interesting laboratory test, not seriously to be considered as a helpful method of diagnosis. The chief results of all of this uncorrelated labor may be briefly summed up in the statement that the iodine reaction occurs with great constancy in conditions of toxemia, both bacterial and non-bacterial; that it signifies a lowered vitality of the iodophilous cells, and that its exact nature is not definitely understood. Of bacterial toxemias productive of iodophilia, such conditions as pyogenic abscess, general sepsis, and many of the specific febrile infections are the underlying factors; while iodophilia excited by non-bacterial or chemical toxemia may develop, for example, in diabetes mellitus, in leukemia, in dyspnea, in acetanilid poisoning, after ether narcosis, and, perhaps, in high-grade anemias. In passing it is of interest to recall Goldberger's success in producing iodophilia in dogs by the administration of peptone and also by rendering them diabetic by pancreatectomy. Kaminer observed the reaction in animals injected with the toxins of the pneumococcus, the Klebs-Löffler bacillus, the Eberth bacillus, and various pyogenic bacteria; and Spezia noted the change in animals treated with large doses of glucose and of olive oil, given subcutaneously.

Within the past four or five years the subject of iodophilia has been studied with renewed interest, especially in this country, where excellent work has been reported by Cabot and Locke, Dunham, Dunn, and Keen. Abroad similar investigations have been carried on, notably by Mannaberg, Loeper, Schmidt, Gulland, and Reich. But in spite of these efforts little new light has been thrown on the subject of the iodine reaction, the precise nature and many phases of which still remain moot points, or, indeed, have been quite unproved.

OBJECTS AND TECHNIQUE. The objects of this inquiry are to study, from both clinical and laboratory viewpoints, this leukocytic reaction to iodine, and by correlating the data thus obtained, to deduce facts by which the scope and limitations of the test may be established and its true diagnostic value interpreted.

With these objects in view, one hundred patients suffering from various acute infections and chronic disorders have been examined clinically, and notes made of their important symptoms. Blood films, obtained at the time of the bedside examinations, were then stained for the iodine reaction, and in fifty of the cases hemoglobin estimates and counts, both absolute and differential, of the erythrocytes and the leukocytes were also carried out. In fifty of the positive reactions the percentage of iodophiles and of the different types of such cells, described in a following paragraph, were calculated, by examining one hundred leukocytes found in consecutive fields of the microscope.

Thus, the attempt has been made to ascertain the relation and incidence of iodophilia, to investigate the types, degrees, and other characteristics of the reaction; and to study in detail its relation to anemia and to the quantitative and qualitative condition of the leukocytes. In addition to these examinations of pathological bloods, films from healthy subjects were also studied by an identical technique, to serve as controls. In no one of the twenty normal blood specimens, examined as a preliminary step, was a positive reaction noted, and in the numerous controls examined subsequently, as the occasion demanded, the results were uniformly negative.

About one-half of the clinical material was obtained at the German Hospital, where I was fortunate enough to have the assistance of Dr. William Warren and Dr. J. Bernard Mencke, internes at that Institution, in verifying details of the case histories; the remainder of the cases were examined at the Jefferson Medical College Hospital and at the Philadelphia General Hospital.

The technique used in the following tests was essentially that advised by Ehrlich—the treatment of the air-dried blood film, unfixed and spread upon a cover-glass, with a reagent consisting of iodine 1, potassium iodide 5, and distilled water 100 parts, to which 50 parts of gum arabic are added, in order to give the mixture a syrupy consistence. The specimen is simply mounted upon a glass slide by means of a drop of this reagent, and then examined microscopically with a one-twelfth inch oil immersion objective after a lapse of about five minutes. Five minutes' exposure of the film to the fumes of iodine crystals (Zollikofer's method) and then mounting in levulose gives equally satisfactory results. Prolonged treatment with iodine does not develop iodophilia in a normal blood film, nor does it appear to intensify a reaction produced by a brief exposure to the reagent.

In about one-half of the differential counts Wright's stain was used and in the others the iodine stain afforded clear differentiation of the various types of leukocytes and erythroblasts.

Dare's hemoglobinometer and the Thoma-Zeiss hemocytometer were used in the hemoglobin and cellular estimates, respectively.

SUMMARY OF RESULTS IN 120 CASES. Aside from uniformly negative results in testing twenty normal bloods for iodophilia, the reaction was tried with one hundred pathological bloods, of which it was positive in sixty-four. In all of these positive cases it was reasonable to attribute the result of the test either to the effect of frank pyogenic sepsis or to the influence of chemical toxemia. The results of these tests have been briefly summarized in the accompanying table.

Of twenty-six cases of *enteric fever*, the nine which showed iodophilia were types of severe infection with the Eberth bacillus, complicated in two instances by pneumonia, and in one each by local peritonitis, by free intestinal hemorrhage, and by general septicemia. Of eleven uncomplicated enterics examined during and after the fourth week of the disease, two reacted positively.

In enteric fever iodophilia may develop as the result of an intense typhoid infection, or it may betray the presence of such complicating factors as pneumonia, purulent lesions, peritonitis, and, perhaps, high-grade secondary anemia. In this disease the iodine reaction has no specific diagnostic value, since it may be symptomatic of many diverse conditions. In uncomplicated cases the presence of a well-marked iodine reaction on the part of a large proportion of the leukocytes is significant of an intense infection. In obviously complicated cases, a positive reaction is merely corroborative of the more definite clinical findings.

Of thirty *purulent* and *septic* cases, the reaction was positive in all, its intensity in these conditions probably depending upon the virulence of the infecting principle rather than upon the extent of the suppuration and the identity of the invading bacteria. In abscess free permeability of the limiting pyogenic membrane favors the occurrence of the reaction, while thorough walling off of the pus focus, as well as adequate drainage, is not attended by iodophilia. In this class of cases are included appendical abscess and gangrene, pelvic abscess, gall-bladder empyema, hepatic abscess, purulent peritonitis, and general septicemia. In addition to uniformly positive findings in sixteen cases of purulent and gangrenous appendicitis, iodophilia was found also in two cases of simple catarrhal inflammation of the appendix, the reaction being very conspicuous in one instance, and very faint, though unmistakable, in the other. In spite of careful search for a reason for the reaction in these instances, none was discovered—neither patient was septic, anemic, strikingly febrile, or handicapped by any sort of complication. The results, therefore, must remain unexplained, unfortunately to the detriment of the test as a criterion for discriminating the catarrhal and the suppurative forms of the disease.

In *croupous pneumonia* the seven cases in which the reaction was tried all gave positive results. The blood of these cases was examined during the height of the precritical period of the disease, and gave examples of the most striking types of the reaction encountered in the entire series of cases included in this report.

In no other disease, not even in grave streptococcus septicemia, does so high a degree of iodophilia develop as that ordinarily met with in the active stages of pneumonia. After crisis the iodophilia begins rapidly to disappear, and in the uncomplicated case does so completely within about forty-eight hours after the critical defervescence. Persistence of the reaction beyond this period may be symptomatic of delayed resolution, of pulmonary abscess, of empyema, or of some other sequel of the pneumococcus infection.

Four cases of *gonorrheal arthritis* showed iodophilia in a decided degree, while, on the other hand, the reaction was wanting in two cases of acute rheumatic fever. The bearing of these results upon the differential diagnosis of these two conditions is too self-evident to call for further comment.

Positive results were also obtained in the following diseases: Acute pneumonic phthisis, carcinoma, pernicious anemia, myelogenous leukemia, diabetes mellitus, and amyloid liver; while, in addition to the diseases already specified, iodophilia was not noted in this list: Endometritis, cholelithiasis, biliary cirrhosis, malarial splenomegaly, ovarian cyst, rickets, and acetanilid poisoning.

SUMMARY OF IODOPHILIA TESTS IN 100 CASES.

Clinical diagnosis.	*Cases.*	*Positive.*	*Negative.*
Enteric fever	26	9	17
Croupous pneumonia	7	7	0
Sepsis; abscess[1]	30	30	0
Tuberculosis[2]	3	1	2
Carcinoma	3	2	1
Gonorrheal arthritis	4	4	0
Rheumatic fever	2	0	2
Primary anemia[3]	5	4	1
Diabetes mellitus	3	3	0
Catarrhal appendicitis	4	2	2
Amyloid liver	2	2	0
Endometritis	2	0	2
Nephroptosis	2	0	2
Cholelithiasis	2	0	2
Biliary cirrhosis	1	0	1
Ovarian cyst	1	0	1
Rickets	1	0	1
Malarial splenomegaly	1	0	1
Acetanilid poisoning	1	0	1

TYPES OF IODOPHILIA. Iodophilia occurs in the cytoplasm of the leukocytes as a diffuse brownish discoloration, as a granular stippling, and as a combination of the two. The change is restricted absolutely to the protoplasm of the cells and does not implicate their nuclear structure, though the latter may be mottled with discrete refractile points which, at first glance, superficially resemble the iodophile reaction. The color of the reaction ranges within very wide limits—from a delicate shade of tan to a deep mahogany red, in the diffuse type, to almost black, in the granular variety. The general rule holds true, that the smaller the iodophilous cell the deeper its color, this tendency being similar to that prevailing in other methods of blood staining; with the Ehrlich or with the Romanowsky stain, for example, the smaller neutrophiles with densely crowded granules in their cell body stain more conspicuously than their larger prototypes whose granules are relatively few in number and sparsely distributed.

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[1] Including general sepsis, purulent peritonitis, appendical abscess and gangrene, gall-bladder empyema, pelvic abscess, pyosalpinx, purulent colitis, hepatic abscess, and osteomyelitis.

[2] Positive in acute pneumonic phthisis; negative in chronic ulcerative phthisis and in tuberculous peritonitis.

[3] Positive in pernicious anemia and in myelogenous leukemia; negative in Hodgkin's disease.

Regarding the relative incidence of the various types of iodophilia, it may be said that simple diffuse staining of the cells and diffuse plus granular reactions occur with about equal frequency, while cells showing a purely granular stippling are exceedingly uncommon. Of the fifty cases of the series studied differentially, twenty-five showed simply diffuse staining, twenty-four both diffuse and granular changes, and the remaining single case purely granular mottling of the protoplasm.

In the *diffuse type* of iodophilia the deepest coloring is generally observed in the neighborhood of the nucleus and at the periphery of the cell, the intervening protoplasm being either of a diffuse, even lighter brown shade, as is the rule in reactions of moderate intensity; or blotched irregularly with deep mahogany colored areas upon a paler undertone, as is the general finding in reactions of more striking intensity. In the *granular type* the individual granules vary in size from that of the most delicate neutrophile to that of the coarsest mast cell; their distribution is generally toward the periphery of the cell; and their shape is spherical or ovoid. Although some of the larger granules may show a ragged, uneven outline, they invariably remain discrete and never fuse into conglomerate masses, as is the apparent tendency of the extracellular bodies of similar morphology.

VARIETIES OF LEUKOCYTES IMPLICATED. In the vast majority of positive reactions the polynuclear neutrophile cells, and this type of leukocytes only, show the iodine changes. In but one case did I find these cells unaffected in blood containing other iodophilous leukocytes. Less commonly the lymphocytes, especially the small variety, are iodophilous, and occasionally these cells bear upon their extreme outer margin three or four coarse, deep, mahogany colored spheres conspicuously contrasting with the scanty rim of cell-body to which they cling. Other lymphocytes show a cytoplasm sprinkled with delicate granules similar in size, in density, and in distribution to those occurring in a delicately stippled, basic erythrocyte. Next in frequency the neutrophile myelocytes are affected, though not so commonly as would be naturally expected, from their close biological relation to the polynuclear neutrophiles. Very rarely an occasional eosinophile is found to be iodophilous; this I detected in two instances, in each of which the reaction was both diffuse and coarsely granular, but in neither of which were more than 2 per cent. of the total number of leukocytes thus affected. With the exception of these two cases and one instance reported by Zollikofer, iodophilia of the eosinophiles has not been recorded before, so far as I am able to ascertain.

Neither Cabot nor Locke has met with it in their extensive series of cases, and Simon distinctly states that eosinophiles are never implicated. The Continental investigators also seem not to have noticed the reaction in this variety of cells. I have never seen an iodine-stained mast cell.

Of fifty differential counts in positive reactions, there were ten in which leukocytes other than polynuclear neutrophiles showed iodophilia. The identity of these cells and their proportion to the total number of iodophiles are given herewith.

TYPES AND PERCENTAGES OF IODOPHILES OTHER THAN POLYNUCLEAR NEUTROPHILES IN 50 POSITIVE REACTIONS.

No.	*Diagnosis.*	*Type.*	*Per cent.*
2.	Purulent peritonitis	L. L.[1] Trans.[2]	3.5 2.0
7.	Appendical abscess and gangrene	S. L.[3]	1.0
11.	Appendical abscess	Eosin[4]	2.0
12.	Acute pneumonic phthisis	S. L. Trans.	4.0 1.0
15.	Croupous pneumonia	Myel.[5] Eosin.	1.0 2.0
22.	Enteric fever	Myel.	2.0
34.	Croupous penumonia	Myel.	2.0
45.	Sepsis	S. L.	5.0
59.	Diabetes mellitus	S. L.	1.0
82.	Enteric fever	S. L.	2.0

Although leukocyte débris, much of it presumably of plasmolytic origin, commonly stains with the iodine reagent, the frankly degenerate leukocyte, so long as it remains structurally intact, does not

[1] Large lymphocyte.
[2] Transitional form.
[3] Small lymphocyte.
[4] Eosinophile.
[5] Myelocyte.

appear thus to react. In many of the bloods examined vacuolated but otherwise normal, neutrophiles were found, sometimes in abundance, but in none of these examples of early plasmolysis was the slightest iodine reaction detected. This peculiarity I have studied with particular interest, for it was natural to believe that beginning cell destruction would be attended with more or less iodophilia. It seems, however, that the latter is related to some chemical change in the cells, of which their microscopic signs of degeneracy are by no means a criterion.

Since the above paragraph was written I have had the opportunity to study a case of acute lymphatic leukemia whose blood contained an extraordinarily large number of mitotic lymphocytes. In several of these cells (both in those with monaster and with diaster figures) fine iodophilous stippling was observed, and diffuse iodophilia of the polynuclear neutrophiles was also noted.

Intensity of the Reaction. For clinical purposes it simplifies matters to gage the intensity of the reaction rather by the depth of color shown by the iodophilous cells than by their actual number. Thus if the prevailing shade be deep brown or mahogany, it is convenient to designate the reaction as "intense," if light brown as "moderate," and if dull orange as "faint." It cannot be denied that the troublesome "personal equation" of the examiner must be reckoned with in judging these criteria, yet, on the whole, those familiar with the various phases of the reaction employ them with a surprising uniformity of results.

Of the fifty examples of positive tests analyzed with reference to the intensity of the reaction, fifteen were labelled intense, twenty-two moderate, and thirteen faint, according to the standards above noted.

From this analysis it was found that, while usually a striking color intensity means also a high numerical degree of iodophilia, it cannot always be said that the qualitative and the quantitative changes progress *pari passu*. It is significant, however, that in no intense reaction of this series did the proportion of iodophilous leukocytes fall below 25 per cent. of the total number of cells examined, and that in most of the cases their percentage approximated, and often exceeded, fifty. This is shown in the following summary, which gives an idea of the abundance of iodine-stained cells in each of the three grades of the reaction.

PERCENTAGE OF IODOPHILES IN 50 CONSECUTIVE POSITIVE REACTIONS.

Grade of Reaction	*No. of cases and per cent. of iodophiles.*			*Total.*
	+ 50 per cent.	25 to 50 per cent.	— 25 per cent.	
Intense	9 cases	6 cases	0 cases	15
Moderate	3 "	12 "	7 "	22
Faint	1 "	6 "	6 "	13

The degree of iodophilia in any given blood film reacting positively is determined partly by the activity of the toxemia in the individual and partly by the inherent vulnerability of the cells. An abundance of deeply stained cells is commonly met with in septic cases with febrile disturbances, prostration, and other signs of severe infection, and in such instances it seems reasonable to regard the reaction as a rough gage of the toxemia. Well-defined iodophilia may also occur in those who suffer from nonseptic diseases and who, though acutely ill, show no signs of a grave systemic intoxication; in these cases it is possible that the cells are pathologically hypersensitive and in consequence are highly susceptible to the action of the staining reagent. In either event it is not unreasonable to attribute to individual cell peculiarities a certain influence in determining the incidence and the intensity of the reaction. As already remarked, the technique of staining, as ordinarily practised in clinical work, has no influence upon the intensity of a positive reaction—a film stains no more intensely after twenty-four hours' exposure to the reagent than after twenty-four minutes. This point I have repeatedly verified in the series of cases under discussion.

RELATION BETWEEN IODOPHILIA AND LEUKOCYTOSIS. In order to determine, if possible, this question, thirty-five consecutive cases with leukocytosis and the same number without leukocytosis are taken as a basis of the deductions. In this connection it should be explained that counts of 10,000 per cubic millimeter or higher are regarded as leukocytosis, and those below this figure as normal or leukopenic, as the case may be.

The mere question of leukocytosis has not, *per se*, the slightest bearing upon the production of iodophilia. This somewhat broad statement can be repeatedly verified by anyone who has done much work with the reaction and who, before drawing conclusions, takes the precaution to investigate the individual case from the clinical as well as the laboratory standpoint. Toxemia, not the leukocyte range, is the factor of the reaction, and this being the case, it is easy to understand why the blood of a profoundly septic individual may show intense iodophilia with decided leukopenia, while high leukocytosis without iodophilia is not incompatible with a disease exciting a toxemia sufficient to stimulate the cells' overproduction but not intense enough nor of the requisite character to affect them structurally.

It is true that a study of *averages* (which may mislead or guide according to one's viewpoint) shows beyond doubt that iodophilia is far more frequent in connection with leukocytosis than it is with normal counts. But this simply means that, as a rule, leukocytoses are symptomatic of more or less toxemia and that normal counts generally mean an absence of such a condition. Thus in the cases under consideration those with leukocytosis showed 88.5 per cent. of positive iodine reactions, while those with normal or subnormal counts gave but 27.1 per cent. Detailed analysis of these figures shows that twenty-four of the thirty-one positive reactions with high leukocyte estimates were associated with definite, sometimes most decided, sepsis, symptomatic of appendical abscess and gangrene, gall-bladder empyema, pelvic abscess, pyosalpinx, hepatic abscess, puerperal sepsis, phthisis with cavity formation, croupous pneumonia, and septic enteric fever; of the remaining seven positive reactions, the clinical pictures were those of diabetes mellitus, amyloid liver, carcinoma, malarial cachexia, and uncomplicated enteric fever. The four negative reactions in this class of cases were met with in rheumatic fever and in biliary cirrhosis of the liver.

Of the thirty-five cases without leukocytosis, grave sepsis figured in nine of the positive results, well-marked infections in seven, and in the remaining four, acute non-suppurative appendicitis, and pernicious anemia, each two cases. Of the fifteen negative tests in this group none was, in a clinical sense, obviously toxic, the diagnoses being as follows: uncomplicated enteric fever in four instances nephroptosis in two; gallstone colic in two; and enteralgia, ovarian cyst, gastric cancer, rickets, uterine hemorrhage, tuberculous peritonitis, and Hodgkin's disease in a single case each.

RELATION OF IODOPHILIA TO QUALITATIVE LEUKOCYTE CHANGES. This relationship was investigated by comparing, individually and collectively, the differential counts in fifty consecutive positive reactions with the degree of the latter, judged by the standards above explained. Taking as a qualitative index the percentage of polynuclear neutrophiles, the proportions of this type of leukocytes, to the other forms of cells in the three different grades of iodophilia may be thus expressed:

PERCENTAGE OF POLYNUCLEAR NEUTROPHILES IN 50 CONSECUTIVE POSITIVE REACTIONS.

	No. of cases and per cent. of polynuclear neutrophiles.		
Grade of reaction.	*Cases.*	*Range.*	*Average.*
Intense	15	64 to 91	81.2
Moderate	22	71 to 88	82.7
Faint	13	68 to 87	71.4

These results suggest that in faint reactions the differential leukocyte counts more nearly approach the normal standard than in well-marked reactions. That the latter show higher polynuclear figures is to be expected, for this grade of iodophilia is very commonly accompanied by absolute leukocytosis, which, of course, means pathologically high numbers of polynuclears, the very cells most susceptible to iodine. And in most instances it must be also assumed that the cells' resistance is lowered, owing to the deleterious effects of the toxic factors responsible for their unusual abundance in the circulating blood. But it is going too far to presume that the higher the polynuclear percentage the more intense the iodophilia in the *individual* case. Though this may be true of the average, it is not always applicable in the isolated instance, since occasionally one meets with a most striking degree of iodophilia in blood showing a normal or even a subnormal number of polynuclear neutrophile cells. In this connection it may be recalled that Kaminer has shown that polynuclear iodophilia of the bone-marrow and of the peripheral blood are intimately related. This worker proved that in animals circulatory iodophilia of the polynuclear neutrophiles was invariably associated with a similar marrow change, and that in normal animals the neutrophiles of the marrow never showed the slightest evidence of susceptibility to iodine. The association of circulatory and myeloid iodophilia I have observed in one instance—a case ot acute lymphatic leukemia whose blood during life and whose bone-marrow after death showed lymphocytic and neutrophilic iodine-stained cells.

Relation between Iodophilia and Anemia. The study of this phase of the reaction is based upon fifty cases in which the percentage of hemoglobin and the number of erythrocytes were determined. In the analysis of these data, cases with hemoglobin figures of 60 per cent. or less and erythrocyte counts of 3,000,000 or lower were arbitrarily classed as anemic, while those with blood counts higher than these standards were considered non-anemic, ten of the counts falling in the former, and forty in the latter, group.

Anemia cannot be regarded in any strict sense as a factor of iodophilia, for just as striking reactions are met with in patients with perfectly normal counts as in those with acute, high-grade anemia. Even if it be assumed that there are actively toxic principles at work in certain anemias, notably in those of the pernicious type, the deleterious effects of such substance cannot be potently directed toward the leukocytes, if the susceptibility of these cells to iodine be taken as a sign of such an effect.

In typical instances of primary pernicious anemia, with extreme blood deterioration and the distinctive hall-mark of a megaloblastic blood picture, the reaction, when indeed one occurs, is not comparable in intensity to one provoked by, say, a case of frank septicemia. In repeated examinations of two cases of Addisonian anemia I have been unable to find anything more definite than an extremely faint degree of diffuse iodophilia, affecting a minimun of 14 per cent. of the leukocytes, and a maximum of 40 per cent. The hemoglobin ranged in these two cases between 24 and 40 per cent., and the erythrocytes between 670,000 and 2,060,000 per cubic millimeter.

In the present series the difference between the incidence of iodophilia in anemic and non-anemic cases was too trivial to be seriously considered. The reaction was present in seven (70 per cent.)

of the ten anemic cases, and in thirty (75 per cent.) of the forty non-anemic. In every instance some adequate toxic factor existed, aside from the question of anemia, to account for the iodophilia when it occurred. In view of this experience, I am unable to subscribe to Hofbauer's view that the intensity of the reaction is proportionate to the severity of the anemia with which it is associated. Nor is it easy to put faith in this author's opinion that the occurrence of iodophilia in anemic conditions is of unfavorable prognosis. However, I cannot present data to fortify this view, which perhaps will have to pass as merely a personal skepticism.

Relation between Iodophilia and Pyrexia. From a study of fifty-six cases in which the temperature was taken at the time of the blood examination, it is not possible to substantiate Kaminer's statement as to the active part taken by fever in the production of iodophilia. Of the present series, twenty-four patients had fever ranging between 101.3° and 105° F., and in this group seventeen positive and seven negative tests for iodophilia were noted; in the remaining thirty-two patients the temperature ranged from 96.4° to 101.2° F., and of these the reaction was positive in twenty-three and negative in nine. Thus, in these two classes, arbitrarily divided into those with three degrees or more of fever and into those without fever or with less than three degrees, the percentage of positive results was practically identical—70.8 per cent. for the febrile, and 71.8 per cent. for the so-called afebrile group. As an illustration of marked reactions in practically afebrile patients these data may be of interest:

No.	*Diagnosis.*	*Temp.*	*Leukocyte count.*	*Degree of iodophilia.*	
				Intracellular. Per cent.	*Extracellular.* Per cent.
7	Appendical abscess and gangrene	98.4	14,500	42	12
17	Appendical abscess	97.4	9,000	68	10
33	Appendical gangrene	99.1	7,000	76	8
38	Diabetes mellitus	96.4	13,800	24	0
39	Diabetes mellitus	98.	4,000	31	0
44	Amyloid liver	97.4	21,200	43	2

In all of the above patients ample factors of iodophilia existed, as will be seen from the character of the clinical diagnoses.

In comparison with the above, the following tabulation shows seven negative reactions occurring in patients with more or less fever at the time of the test:

No.	*Diagnosis.*	*Temp.*	*Leukocyte count.*
23	Salpingitis	102.4	8,600
36	Biliary cirrhosis	102	10,100
46	Endometritis	102.2	6,000
89	Enteric fever	100.3	4,500
61	Enteric fever	102	9,000
64	Enteric fever	101.3	6,000
72	Enteric fever	104	8,000

The underlying cause of a febrile state—septic intoxication, for example—is to be held responsible for the positive reaction occurring in a febrile patient, but to pyrexia alone can be ascribed no such influence.

Resume. The following conclusions relating to the pathological and clinical phases of iodophilia may be summarized:

1. In the dry blood film intracellular iodophilia indicates a form of leukocyte degeneration of toxic origin and due presumably to an abnormal affinity of the cell glycogen for iodine. The same reaction in the fresh wet blood film is physiological. Extracellular iodine-stained masses in the plasma have no definite pathological significance, so far as can be determined.

2. The toxic factor of the reaction may be absolute and frankly demonstrable, as in pyogenic septicemia and in pneumonia; or it may be indefinite and masked, as in pernicious anemia and in cachectic states.

3. The reaction is restricted to the cytoplasm of the leukocytes, never affecting their nuclear structure. In fully 98 per cent. of all reactions the polynuclear neutrophiles are implicated; in about 20 per cent., other cells, notably the lymphocytes, and, less commonly, the myelocytes also react; in the exceptional instance iodophilous eosinophiles are noted. Diffuse and diffusely granular brown-staining are the prevailing microchemical changes, pure granular stippling being exceedingly rare.

4. The number of iodine-stained cells corresponds roughly to the color intensity of the reaction, 50 per cent. or higher of iodophiles being generally found in a decided, and approximately 25 per cent. in a feeble, reaction.

5. Iodophilia has no direct relation to leukocytosis, to anemia, or to pyrexia. (*a*) Its relative frequency in patients with high leukocyte figures is due to the fact that such cases are generally toxic; a similar toxemia with leukopenia excites just as intense a reaction. (*b*) The grade of anemia in nowise corresponds to the incidence or to the intensity of the reaction. (*c*) Fever, *per se*, has absolutely no effect in causing iodophilia, afebrile cases and those with hyperpyrexia showing an equal percentage of positive results.

6. From a clinical viewpoint, iodophilia is often a helpful, though under no circumstance a diagnostic, sign, and to be of real service to the clinician it should be correlated with every other detail of the clinical picture. Thus interpreted, a positive reaction in a person obviously ill means that the systemic effect of the illness, whatever it may be, is vigorously exerted, in so far as its harmfulness to the patient in question is concerned; in this connection the sign is useful in the study of such diseases as enteric fever, pneumonia, diphtheria, general sepsis, and many of the severe cachexias. Especially is iodophilia significant when associated with a leukopenia symptomatic of overwhelming prostration of the individual; iodophilia plus leukocytosis indicates simply an intense infection with an adequate systemic counteraction.

In the differentiation of various specific clinical entities one must be extremely cautious in accepting iodophilia as a criterion. Personally, I have found the test corroborative in differentiating both gonorrheal arthritis and osteomyelitis from rheumatic fever; pure tuberculosis from tuberculosis with secondary pyogenic invasion; ovarian abscess from ovarian cyst; and amyloid liver from fatty, cirrhotic liver. In distinguishing purulent from non-purulent lesions, it must be recalled that the former always give a positive reaction, unless the abscess is so effectually walled off that toxins cannot reach the circulation; and that the latter give a negative reaction, unless there happens to be some other source of toxemia at work. These possible sources of error are extremely exceptionable, but it cannot be denied that they must be heeded in an occasional instance.

REFERENCES. Cabot and Locke: Journ. of Med. Research, 1902, vii. 43. Czerny: Arch. f. exp. Path. u. Pharmak., 1893, xxxi. 190. Dunham: Boston Med. and Surg. Journ., 1901, cxliv. 580. Dunn: Ibid., 1903, cxlix. 511. Ehrlich: Zeitschr. f. klin. Med., 1883, vi. 33. Goldberger and Weiss: Wien. klin. Wochenschr., 1897, x. 601. Gulland: Brit. Med. Jour., 1904, i. 880. Hofbauer: Centralbl. f. inn. Med., 1900, xxi. 153. Kaminer: Zeitschr. f. klin. Med., 1902, xlvii. 408. Keen: Rapports Prem. Cong. de la Soc. Internat. de Chir., Bruxelles, 1905, 16. Livierato: Arch. f. klin. Med., 1894, liii. 303. Locke: Boston Med. and Surg. Journ., 1902, cxviii. 289. Loeper: Arch. de med. exper. et d'anat. path., 1902, xiv. 576. Mannaberg: Wien. med. Wochenschr., 1902, lii. 594 and 659. Reich: Beitr. z. klin. Chir., 1904, xlii. 277. Schmidt: Inaug. Dissert., Berlin, 1902. Simon: Manual of Clinical Diagnosis, fifth edition., Phila., 1904. Sorochowitsch: Zeitschr. f. klin. Med., 1904, li. 245. Spezia: Lancet, 1903, i. 655 and 1444. Weiss: Wien. klin. Wochenschr., 1897, x. 601. Wolff: Zeitschr. f. klin. Med., 1904, li. 407. Zollikofer: Inaug. Dissert., Berlin, 1899.

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Histological Changes in Uterine Myomata in their Transformation into Fibroid Tumors.

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DURING the past summer together with a large number of other gynecological specimens sent by Dr. B. C. Hirst from his service in the Howard Hospital in this city to the pathological laboratory of the University of Pennsylvania there were about forty fibroid tumors of the uterus of varying size and situation in relation to the uterine wall. Of these thirty-six were examined by the writers, primarily for the purpose of description and record, and subsequently, after Dr. Brooke Anspach had kindly called our attention to the elastica changes in the uterine wall after involution from pregnancy, it was suggested that sections be also stained with a selective stain for the determination of the existence and distribution of elastic tissue as a possible structural constituent. Unfortunately from the mode of our work it has not been found convenient that we should prepare serial sections for direct and close comparison between the appearances given by the ordinary hæmatoxylin and eosin stain used originally in preparation and those afforded by

Weigert's fuchsin and resorcin solution employed for the latter purpose.

The details of the histological findings in the individual specimens are reserved for future presentation with Dr. Hirst in connection with the clinical features of the various cases; but inasmuch as these tumors as a group have seemed suggestive of the series of changes taking place in uterine leiomyomata in their transformation into fibroid tumors, the features of this type are here brought forward separately. In this place the writers wish to express their thanks to Dr. Hirst for permitting such use of the material, and would also acknowledge the' interest and assistance of Dr. Smith in their study of the specimens and in the preparation of this presentation.

In the examination of these tumors a single block of tissue was selected from each, preferably from the border, reaching into the mass of the growth; and it must be accepted that such selections because of their small number and size may not be truly representative of the entire growth in each instance, although in the entire group the error is not likely to be important. Sections from such blocks were originally stained with hematoxylin and eosin, and subsequently other sections from the same block (but not in known relation to the original ones) were stained with Weigert's elastica solution; in some instances new material had to be taken from the tumor mass, but always from the same place as the original block. Studied from such material but two of the tumors would merit the name of true uterine *fibromata*, if by this term is understood that the growth is made up solely of fibrous tissue, and even these two examples exhibit a few scattered muscle spindles in the midst of the dense and finely fibrillar matrix. If one exclude from the class of true leiomyomata such growths as show at least a small presence of connective tissue distributed as investment of the muscle bundles, none of the tumors under examination could be ranked in this histoid group. The great majority of specimens examined by the writers in the present series show a preponderance of muscle elements in the structure, but with the added presence of a variably important amount of connective tissue, which is seen distributed as an investment of the muscle and as an irregular framework in which the larger bloodvessels ramify; this tissue also being found now and again as practically the only constituent of small but definite nodular areas in this or that part of a growth. Of such tumors, usually spoken of as *fibromyomata*, the series included twenty-nine examples. Five were largely fibrous but showed a smaller admixture of muscle elements, perhaps meriting the combination name *myofibromata*.

The writers are inclined to look upon the original type of uterine myomata as represented by the larger subdivision of the group in hand. It seems impossible to exclude as proper to such growths the amount of connective tissue normal to the uterine wall as perivascular connective tissue or as intermuscular septa. Recognizing too that at least in the fairly formed bloodvessel walls there should develop some small amount of elastic tissue it would seem equally impossible to exclude such an occurrence from the unchanged myoma. From the analogy suggested by Anspach's[1] findings that the vascular elastica is overgrown in the walls of uteri which have undergone involution after pregnancy, it cannot seem improbable that in the irregularities of development and life of a myoma at least here and there in the mass similar changes, with overgrowth of the vascular elastica and its extension about the vessel walls into the surrounding tissue, should take place. So too from its normal occurrence in the uterine wall interlacing with the muscle in small amount, it would seem probable that it might in similar fashion be included in the growth of a myoma. In all of the examples of the tumors in the present series staining by Weigert's elastica stain has shown the presence of elastic tissue, ranging from its occurrence only in the vessel coats and in normal amount, to such amounts as would almost justify the use of the term *elastoma* as part of the complete descriptive name of the new growth. It is more richly present in the nodular types of the tumor, rather in the tissue between the nodules than in the latter themselves. It is found only in small amounts, if at all, in the general tissue of the dense fibrous areas of the combined type of fibromyoma, and is similarly absent in the rarer examples in the series of pure fibroma. Occurring in the midst of the tumor tissues, as investments of the muscle, or in greater or smaller masses in the outer coats and outside the coats of the vessels it has been found especially in those myomata which are apparently in process of change to become fibroids (including thus the greater number of specimens of the present series). In many of the vessels its occurrence is no greater in amount and not more irregular than would be regarded as normal. However, where there is evidence of vascular thickening or where obliterative changes are taking place in the vascular walls, it is with uniformity found overgrown, usually quite irregular and commonly extending from the vessel wall in greater or smaller amount into the surrounding fibromuscular tissues. In some cases dense masses, irregularly extending along the course of some vessel, are to be seen, from which smaller lines of the material are projected out into the muscle aiding in the investment of the muscle bundles. Occasionally more compact bunches are seen about the vessel walls, probably the same hyaline material referred to by Anspach. In a few instances the material as it was seen in the fibromuscular substance of the tumor was more or less broken, appearing as small lumps and fragmented threads, the muscular tissue of such areas showing in more or less clear manner granular changes of the protoplasm with fine vacuolation and uncertainty of staining reaction, the fibrous fibrillæ of such places also showing more prominence than in areas or general sections in which such retrogressive appearances of muscle and elastica were absent. Finally, as far as this element is concerned, as above mentioned in the advanced areas of fibrosis and in the pure fibromata, little or no elastica could be detected.

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[1] Transactions Philadelphia Pathological Society, December 14, 1905.

While it is impossilbe to declare positively as to the nature and mode of action of the cause underlying these changes it seems not improbable that in a greater or less measure they are the result of nutritional disturbances connected with vascular changes of a chronic hyperplastic type; an idea which seems corroborated by the findings noted for these growths as far as relates to the bloodvessels and the appearances of the muscle and of the fibrillar material of which the fibroid areas are composed. In the present group the denser and more fibrous types have been tumors which, because of their position (as when almost isolated from the uterine wall beneath the peritoneum), or because of the density of encapsulation, would have suggested the idea that they had received a minimum of nutrition; their dense white tissue, moreover, indicating their relative avascularity. In comparing the bloodvessels of the various sections studied the occurrence of sclerotic thickenings, condensations, and hyaline change which last apparently is in relation with an excessive amount of elastica, is most common in those instances where there are apparent a recession in amount of the muscle and a corresponding increase in the amount of the fibrillar tissue, this latter being in some measure composed of elastic elements. Further, it is to be noted that the denser and more completely fibroid areas do not present vessels comparable in number with that of the vessels of the more muscular portions of such a growth; that their vessels are not conspicuous objects but more often appear as mere endothelial lined channels in the midst of the fibrillar material (as if the outer parts of an original wall of the vessel may have merged and been lost in the surrounding tissue so completely as to be no longer recognized from the latter); and that there often exist evidences of faulty circulation in the occurrence of hemorrhagic foci and pigmentary deposits in the tissues (or occasionally in phagocytic cells) along their course. These dense areas, too, rarely present any number of cells such as can be considered as antecedents of true fibrous tissues; fibroblastic elements being seen if at all rather in less fibrous sections where more muscle persists, and then usually in quantities not suggesting the massive formation of fibroid structure commonly seen in advanced specimens, but rather restricted to the walls and immediate neighborhood of the bloodvessels. Moreover in these dense fibroid areas one commonly encounters a fine interfibrillar granular material which might be thought of as being in part at least a detritus rather than as wholly (as usually interpreted) representing transverse sections of fibrils running opposite to the plane of section. That there is true fibrous tissue formation cannot be doubted from the appearance of the vessel walls in the less dense portions of these growths where the presence of fibroblasts and the outgrowths of elastic tissue are common along the outside of the vessels. It might thus be thought that in the evolution of a fibroid from a myoma there occurs for unknown reason a hyperplastic process in the walls of the bloodvessels leading to an overgrowth of their fibrous elements and at the same time to an increase (in the manner indicated) of the elastic elements of their structure. Eventually, however, such changes occlude the affected vessels and interfere with the nutrition of the parts of the growth in which they are distributed, as an evidence of which perphaps stands the fragmented and altered appearance of this elastic tissue in parts thus changing; and for which too the practical absence of such elastic issue in permanently fibroid areas would argue. Close regard to the fibrillar material of these fibroid areas would indicate too that it presents features suggesting retrogression rather than active formation of true fibrous tissue, that while there are evidences of the true formation of fibrous elements along the course of bloodvessels at an earlier stage these are insufficient to account for the massive fibroid changes frequently seen either locally in the tumor or affecting the whole tumor mass. If such position be assumed there remains for consideration the part taken by the muscle of the original growth. Comparison of the various slides of the present series clearly indicates the fact (to have been expected *a priori*) that the best preserved and developed muscle is to be found in those tumors in which the least vascular alteration is evident, or in those parts of a partially altered myoma where such vascular changes are least marked; and that coincident with the appearance of marked hyperplastic and sclerotic vascular changes and with the assumption of a fibroid character the muscle spindles are apt to show regressive changes of the character of simple atrophy of the cells and of degenerative and necrotic alterations (evinced by undue granularity of of the protoplasm, shrinkage of the nuclei from an oval to a more and more slender rod shape, vacuolization of the protoplasm and faults in the assumption of the stains). Eventually many or all of the muscle elements disappear and there remains behind a tissue whose character while closely approaching the fibrous tissue of a scar differs from the latter in the fineness of its fibrillation, in the absence of cellular elements or of the bellied shape of the fibrils, which would indicate their former cellular character, and by the presence of more or less fine interfibrillar granular material which may in part at least be of the nature of detritus. Often the remnant muscle elements of areas approaching this conditon seem in direct continuity with this fibrillar material; and while such continuity of substance cannot be absolutely insisted upon, the idea that remnants of the muscle are contributing to the fibroid material is strongly suggested. Certainly, no evidences of multiplication of muscle and formation of fibrous tissue from the products is shown in any of the specimens examined by us. The last portion of recognizable muscle constituent aside from such fibrillar remnants is the nucleus, which is often seen isolated or still surrounded by a small amount of protoplasm embedded in the fibroid substance, without any appearance of the features of multiplication but commonly with evidences of retrogression in staining qualities, in size and in the appearance of vacuoles in the nuclear plasm.

(As illustrative of such muscular changes several photomicrographs published in the *Univ. of Penna. Med. Bull.*, March, 1906, were presented, made from a large uterine fibroid which having become parasitic upon the lower border of the omentum had become separated from its uterine attachment entirely and was thus suspended upon the omentum as a pedicle. Through some passive movements of the tumor the omental pedicle had been twisted in seven complete turns and presented an appearance not unlike the umbilical cord. The block of tissue from this growth was taken from the lower portion of the mass, at some distance from the omental attachment at the upper part of the tumor, and extended from the periphery for nearly two centimeters into the interior. At the peripheral portion of the section the tissue is that of a nearly pure myoma, with large perfectly staining muscle spindles; in a slightly deeper portion the presence of a greater proportion of the fibroid material is shown, the muscle spindles are of distinctly smaller size and at places fault of staining and vacuolization of the muscle spindles are evident. In the next deeper portion the large preponderance of fibrillar material is clear, and the apparent continuity of the evidently deteriorated muscle spindles with the fibrillæ of the general matrix is shown; the size of the spindles is materially smaller than in either of the more superficial levels, and isolated nuclei lie in the midst of the finely fibrillar matrix. Arterioles are to be seen, characteristic sclerotic thickening of the wall, a few fibroblasts and plasma cells lying just without the outer portion of the wall and the latter in a large portion of its circumference merging into and practically indistinguishable from the surrounding fibroid matrix. Such a change or where the lumen of the original arteriole is all but obliterated by a deforming endarteritis, represent the common types of vascular changes widely encountered in the specimens under examination and probably underlie the regressive changes of the tissue of the myoma which our observations suggest play an important part in the conversion of the tumor into the fibroid condition.)

As a resumé of the above considerations the following may not be regarded as unjustified:

1. In uterine myomata there is always a certain amount of elastic tissue, either in normal amounts and relations in the bloodvessel walls or sometimes in the tumor tissue, where it is distributed among the bundles of muscle along with fibrous tissue of such septa and muscular investments.

2. Vascular changes of the type of fibrous and elastica hyperplasias are common in such tumors, leading to the thickening of their coats and eventual obliteration of the vessels; and increasing the connective-tissue framework of the tumor in the vicinity of the affected vessels.

3. Probably as a result of nutritive disturbances brought about by such vascular changes this excess of elastica in the surrounding tissues does not maintain an integral condition but deteriorates and eventually disappears.

4. Probably dependent upon the same nutritive disturbances the original muscular elements of the tumor also atrophy, degenerate and necrose and finally disappear as muscle spindles although there is some evidence that the cell wall (corresponding to the sarcolemma of the striated type of muscle) may remain and contribute in a passive manner to the fibrillar material of the final fibroid tissue. The character of the tissue and the relative paucity of fiber-forming young elements is consistent with the idea that the fibrillar tissue of the final uterine fibroid is in a large part not true fibrous connective tissue, and that the general process of transformation is not a progressive but a retrogressive one.

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Observations upon the Form of the Red Blood Corpuscle of Man.

BY HENRY E. RADASCH, M.S., M.D.

IN examining series of slides representing tissues derived from autopsies on fetuses, the writer noted the constant presence and great numbers of red cells that did not possess the classic biconcave shape. In reviewing the literature in regard to the varying shape the following data were obtained:

As early as 1719 Leeuwenhoeck,[1] the earliest student of the blood, called attention to red blood corpuscles of a globular form which he termed "globuli sanguinis." Some of these possessed an indentation or sinus, apparently conforming to the bell-shape of the later writers. Even with the poor facilities for such work the general correctness of his observations was confirmed by Muys[3] in 1741, and Fontana[5] in 1787. Senac,[2] however, in 1749 described the cells as flattened spheres or "lenticular disks," and from this time the general consensus of opinion seemed to point to the disk form. In 1821 the studies of Dumas[31] led him to describe the red cells as flattened, disk-like structures, while Schmidt,[4] in 1822, called them "compressed spheres with flattened sides and raised edges." In 1832 Joh. Mueller[6] described these cells as *coin-shaped*, but he was in error when he considered the concavity a small nucleus. Hewson's[7] description may be summed up in the words "*as flat as a guinea;*" Wagner[8] (1832), Schultz[9] (1836), Henle[11] (1831), Funke[10] (1858), Ecker[12] (1851 and 1859) agreed that the red corpuscles had a biconcave form. In 1857, Leydig[13] gave drawings of the bell-shaped cells, but did not accompany them with any description.

Rudolph Wagner[14] (1838) described the bell-shaped cells, and in 1865, M. Schultz[15] found that blood drawn from the finger and preserved in a warming chamber under proper conditions of moisture and temperature (40° C.), for two to three hours, exhibited very few biconcave cells, whereas if the blood was preserved for several days under the same conditions but heated to 52° C. the cells became globular in form. From a study of his own blood and that of a number of other persons he concluded that the usual form of the red corpuscle was that of a "Glocke," or bell. In addition to these cells he found a number of globular corpuscles 5 to 6 microns in diameter.

In 1888, S. H. Gage,[16] in his studies on the blood of lampreys, found that the colored blood cells were bell-shaped just as Brass[17] in his atlas of 1879 had figured them. Dekhuyzen[18] somewhat later gave a good description in his work on Petromyzon fluvialis. This is briefly given as follows: "The fixed or living blood cells are bell-shaped and possess a rather deep opening, the *oral* concavity. This is a rather wide, circular mouth but may be triangular or slit-like. At the aboral pole a second, though insignificant, depression, the *aboral* concavity, is at times found. If the latter is pronounced the cell is no longer bell-shaped but biconcave. These cells when examined from above are suboval and almost round." This writer suggests the name *chromocraters*.

He found that the mammalian cells at one time in their history are chromocraters and that they extrude their nuclei at the oral concavity and retain their bell-shape as stated also by Howel.[19] When the oral depression becomes shallow the aboral concavity disappears. Dekhuyzen states that the bell-shaped cells can very readily be studied by drawing the blood into a 1 per cent. solution of osmic acid, in which the cells are instantly fixed.

In 1902, Weidenreich,[20] in his work on the blood of the hedgehog, found the cells nearly globular in form with one surface slightly depressed, giving a concavo-convex shape to these corpuscles. He studied fresh human blood by preserving it in a warming chamber as a hanging drop, and found many bell-shaped cells; these varied from shallow to deep. He noted that rouleaux formation occurred only when the blood became still, cool, and condensed. If sodium chloride be previously added rouleaux formation does not occur. If the blood be mixed with a 0.6 per cent. solution of sodium chloride the cells are all bell-shaped. Weidenreich studied the blood in the living circulating condition in the omentum of the rabbit and found the bell-shaped cells most beautifully exemplified. The same was found later by Lewis[24] in his studies of the erythrocytes in the omentum of the guinea-pig.

Weidenreich's experiments upon the red cells with salt solutions resulted as follows: When a 0.6 to 0.65 per cent. solution of sodium chloride is used nearly all of the cells have the bell form. If the strength is decreased to 0.3 per cent., then upon the addition of this to the blood the cells become globular. If a 1 per cent. solution is used the cells become morular and shrink, while if the solution is 2 per cent. or stronger, the cells swell and the hemoglobin is dissolved.

This writer gives the following dimensions for the bell-shaped cells: greatest diameter, 7.0 microns; diameter of cavity, 3.0 microns; height of cell, 4.0 microns; height of cavity, 2.5 microns; thickness of wall at apex 2.0 microns; thickness of wall at base 1.5 microns.

Hamburger,[21] in 1898, thought that possibly the oxygen-bearing cells were bell-shaped while those laden with carbon dioxide were globular. Weidenreich does not entertain the same opinion but considers the difference in shape due to the difference in density of the blood going to and leaving the organs; the blood entering is richer in salts and of a greater density, therefore the cells are bell-shaped, while the blood leaving the organs is poorer in salts and less dense than before, thus accounting for the globular form.

Von Ebner[22] found by keeping the blood warm and active that the bell-shape was retained. Rindfleisch[23] in his work upon the bone-marrow noticed that most of the cells were bell-shaped and nucleated and that those which lost their nuclei retained the bell form. He holds that this form is characteristic of young cells.

Jolly[25] states that although the biconcave cells seem to be the normal form the bell-shaped cells were present in the circulating blood, representing modifications rather than alterations. His fresh cover-slip preparations were not successful as far as the bell-shaped cells were concerned but Weidenreich[26] considers the result due to very slow manipulation. Jolly found that fresh blood fixed in a 1 per cent. solution of osmic acid contained mostly bell-shaped corpuscles, a few globular cells and others of an intermediate shape but *no biconcave elements.*

So far very little mention is made in text-books of bell-shaped red cells, except by Stöhr,[27] Köllicker,[29] and the writer.[30] Sobotta[28] mentions that spherical cells are occasionally seen. Weidenreich found bell-shaped cells in tissues and stated that "their presence here should not alone be taken as conclusive proof of their shape as one could not be certain that swelling or shrinkage had not been caused by the fixative."

After this review of the literature we find that the earliest accounts of the red cells ascribes to them a bell-shape. Since then opinions have been divided, but it seems that considerable weighty proof has been forthcoming to substantiate the early description. Experiments upon the fresh blood that have been carried out with sodium chloride seem of little importance so far as shape is concerned. The study of the blood in the circulation, the rapid preparation of fresh spreads, and the fixation in osmic acid solution are the points that must be considered. In addition to these the writer desires to bring forward the importance of their presence in great numbers in fixed tissues.

Weidenreich's statement that the presence of the bell-shaped cells in tissues may be due to swelling or shrinkage caused by the "fixing agent" seems entirely too broad and is apparently a blow to the theory of fixatives. Such agents should fix a cell practically instantaneously. Agents that distort or alter the shape of the most delicate cells are not considered good fixing agents and are quickly relegated to oblivion. The changes caused by the salt solutions were changes due to slight alteration in densities and not to fixation. The action of 1 per cent. osmic acid solution is, without doubt, that of a very satisfactory fixing agent and exhibits the red cells as bell-shaped structures, as the writer, after repeated trials, has constantly found. The theory of its action is "fixation with the exclusion of air." If the air is allowed to come into contact with the bells they immediately collapse to the biconcave form and as such are usually studied in the ordinary preparations. If the exclusion of air is essential then the presence of great numbers of bell-shaped red cells is to be expected in properly fixed tissues. Another thing to be borne in mind is the suggestion of Rindfleisch, that the bells, "Glocken," represent young cells.

The tissues studied were derived from about twelve autopsies performed upon fetuses, from five months to term, and upon one infant eleven days old. The tissues were fixed in Heidenhain's solution (a 0.5 per cent. sodium chloride solution saturated with bichloride of mercury). Some of the tissues were fixed in this solution after the addition of 5 per cent. of glacial acetic acid but no difference in the red cells of the two series could be discerned. Sections were cut at 5 and 10 microns, prepared according to the usual laboratory methods and stained with hematoxylin and eosin and hematoxylin and van Gieson.

Although the number of bell-shaped cells under the one-sixth objective seemed large it was further increased under the one-twelfth oil immersion. More attention was paid to the blood-making organ the spleen, and then to the liver, placenta, kidneys and lungs. The study of the placenta was of special interest as it gave an opportunity to note the condition of the cells in both mother and fetus. A few other tissues were also studied in order to confirm the condition in the principal organs.

The spleens are all well filled with blood but even under these circumstances the examination of the pulp is not very difficult in thin sections. Careful examination shows that the bulk of the cells, 80 to 90 per cent., are of the bell-shape and the remainder biconcave. The latter are located chiefly at the margins of the sections. Theoretically these should have been the best fixed, but as they were in contact with the air they collapsed to the biconcave form and were fixed as such, a condition that was to be expected. Globular cells are absent. In all but two of the spleens studied the cells were all well formed and large, averaging 5 to 8 microns in height and 7 to 9 microns in breadth. In the remaining two cases they were shallow, averaging only 3.5 to 4 microns in height.

In the placentas the number of the bell-shaped cells in the intervillous spaces is about the same as in the spleens. This is of especial interest, as these corpuscles represent the maternal blood. The youngest placenta shows nearly all of this form in the villi (fetal blood) and also in the intervillous spaces. In the vessels of the villi the cells are often too densely packed to show individual outline, but in those less crowded they are mostly of the bell-shape, the percentage not falling below 75.

The lung sections show materially the same condition. In addition to the cells in the bloodvessels many red corpuscles are seen in the air-sacs and most of these are of the same form as those within the vessels. The form of the cells in these areas first drew attention to the departure from the biconcave form. The blood in the kidneys does not differ from that contained in the lungs. The bell-shaped cells appear in the vessels of the perirenal fat and even in the exposed vessels.

In the liver the fixation of the cells is not as good as in the other tissues. A large number of the cells show disintegration. As the hepatic cells are well fixed this action is probably due to the hemolytic action of the bile. The unaffected cells, though, are of the bell-shape. The vessels of the umbilical cord contain quite a few cells and these are of the usual bell-shape. As these are of the fetal circulation their presence simply confirms the condition of the erythrocytes in the above organs.

Although the foregoing tissues received most attention sections here and there of the lip, tongue, stomach, esophagus, trachea, adrenal, eyeball, lymph node, parotid, pancreas, appendix, bladder, colon, and several unrecognizable tissues were examined with the results above given. Even in the lumen of the trachea a number of erythrocytes were noted and these exhibited the characteristic bell-shape.

Although the theory of stagnation and condensation has been advanced as the cause of the collapse of the bell-shaped cells it seems that the above results do not bear this out. These tissues were not removed until some time after death and yet the majority of the erythrocytes do not exhibit the biconcave shape. If the cells are biconcave in the circulating blood why should they not be the the same in fixed preparations? The bell-shape as seen above cannot be due to any alteration effected by the fixative as the results are entirely too uniform in all portions of the sections. If the fixing solution had caused swelling the peripheral cells should show this most markedly but the reverse in the case. Those met first by the fixative had already collapsed as a result of contact with the air, whereas those deeper were instantly fixed before the air could possibly reach them. The density of a saturated solution of bichloride of mercury is too great to cause such a slight alteration in the biconcave cells, if we were to grant for the sake of argument that the cells are really biconcave. The cells would be distorted and not uniform. Unless the fixing agent acts instantly the results in the various portions of the sections will not be even.

Weidenreich, in his discussion of Jolly's results, maintains that if the cells are biconcave the fixative will preserve them in that condition without alteration. This he tends to prove by the following experiments: (*a*) drawing blood into a 1 per cent. solution of osmic acid with the exclusion of air, and (*b*) fixation of the blood that has already been exposed to the air. In the former case the cells are all of the bell-shape while in the latter they are all biconcave, before and after fixation. Jolly's work seems to support rather than argue against the bell-shape.

In making a study of the measurements taken a surprisingly large number of the cells were above the average diameter of the red cell as it is usually given. They are all quite tall, the shallow cells having been observed in large numbers in but two of the cases. In comparing the measurements obtained with those given by Weidenreich and referred to by Lewis,[24] the writer finds his somewhat larger. The dimensions obtained are as follows: greatest diameter, 7.8 microns; diameter of cavity, 4.6 microns; height of cell, 5.2 microns; height of cavity, 3.0 microns; thickness of wall at apex, 2.62 microns; thickness of wall at base, 1.6 microns.

CONCLUSIONS: 1. The majority, if not all, of the circulating cells are bell-shaped and not biconcave. Their presence in the adult body, as well as in that of the fetus, is shown by a study of the placenta.

2. Their presence in the fetus and infant seems undoubted, as is shown by their abundance and uniformity in shape and size, in fixed tissues.

3. Upon contact with air the bell-shape is changed to the biconcave, the result of collapse. This is shown by the fixation of blood that has not been exposed to the air, on the one hand, and blood that has been so exposed, on the other.

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BIBLIOGRAPHY.

1. Leeuwenhoeck. Cited by Weidenreich.
2. Senac. Traité de la Structure de Coeur, tome iii, livre v.
3. Muys. Quoted by Weidenreich.
4. Schmidt, J. C. Ueber die Blutkoerner.
5. Fontana. Cited by Weidenreich.
6. Mueller, Joh. Physiologie I, Poppendorff Annalen.
7. Hewson. Experimental Inquiries, Part III.
8. Wagner. Vergleich. Physiologie des Blutes.
9. Schultz, C. H. Das System der Zirkulation.
10. Funke. Atlas der Physiol. Chemie.
11. Henle. Allgemeine Anatomie.
12. Ecker. Cited by Weidenreich.
13. Leydig. Lehrburch der Histologie.
14. Wagner. Beitr. zum vergleich. Physiologie, vol. ii.
15. Schultz, M. Arch. f. mic. Anatomie, vol. i.
16. Gage, S. H. Proc. Amer. Mic. Soc., 1888, vol. x.
17. Brass. Atlas der nor. Gewebslehre der Menachen.
18. Dekhuyzen. Anat. Anzeiger, vol. xv.
19. Howel. Jour. Morphology, vol. iv.
20. Weidenreich. Arch. mic. Anatomie, vol. lxi.
21. Hamburger. Deutsch. Zeitsch. f. Thiermed., vol. ii.
22. von Ebner. Koellicker's Handbuch, 1902.
23. Rindfleisch. Arch. mic. Anatomie, vol. xvii.

24. Lewis, F. T. Jour. Med. Research, 1903-4.
25. Jolly, J. Comp. rend. de Soc. de Biol., Paris, tome lviii.
26. Weidenreich. Anat. Anzeiger, xxvii, No. 24.
27. Stöhr. Lehrbuch der Histologie, 1905, 10th German edition.
28. Sobotta. Hand Atlas of Human Histology, 1902, American edition.
29. Köllicker. Handbuch der Gewebslehre, 1905.
30. Radasch. A Compend of Histology, 1905.
31. Dumas. Cited by Weidenreich.

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Mett's Method for Estimating the Activity of Pepsin.

BY JOSEPH SAILER, M.D., AND CLIFFORD B. FARR, M.D.

WHILE the methods for the estimation of the total acidity, free acid, etc., in the gastric contents have long been sufficiently perfected for satisfactory clinical use, the same cannot be said of the quantitative methods of estimating pepsin. The belief current among most stomach specialists, that pepsin is rarely at fault, and then only when the hydrochloric acid is much reduced or absent, has discouraged activity in this direction. Nierenstein and Schiff (*Arch. f. Verdauungskrank.*, vol. viii, 1902) and others have shown, however, that "diluting secretion, pepsin secretion, and hydrochloric acid secretion are to be regarded as three distinct expressions of the secretory activity of the glandular parenchyma."

Within recent years two promising methods for the clinical estimation of pepsin have come into prominence, those of Hammerschlag and Mett. The former has been widely tried, but on the whole has not been very favorably received. One of us has used it rather extensively with considerable satisfaction, but now prefers the Mett method, as it is simpler and more accurate. The Hammerschlag method (*Intern. klinische Rundschau*, 1894) is open to all the objections raised against the Esbach method of estimating albumin, as well as to others, which it shares in common with Mett's and other pepsin methods. A very good review of the literature of Hammerschlag's method may be found in the article of Robin, in the *Archiv. f. Verdauungskrankheiten*, 1904.

Mett's method (*Contribution à l'Innervation de la Glande sous Stomacale*, St. Petersburg, 1889) has been employed in Pawlow's laboratory in St. Petersburg since 1889, but was introduced into clinical use by Linoissier (*Journ. de Physiol. et de Path. generale*, 1889) ten years later, or five years after Hammerschlag's method was published. Mett's original article is not accessible, except in Russian, but a good description of the method is found in Pawlow's *Work of the Digestive Glands*, p. 25, London, 1902, from which we quote.

"It consists in this: Fluid egg-white is sucked up into a fine glass tube of 1 to 2 mm. lumen, and coagulated therein at a definite temperature (95° C.). The tube is then cut into small pieces, which are placed in 1 or 2 c.c. of the fluid to be investigated. The whole is kept in the thermostat at 37° C., and requires no further watching. Solution of the proteid occurs at the ends of the small glass tubes. After the termination of a certain period (ten hours) the lengths of the pieces of tube, and of the undigested ends of the proteid column, are measured off with the aid of a millimeter scale and a microscope of low magnifying power. The difference gives the length of the digested proteid cylinders in millimeters and fractions of millimeters"

Experiments in the Pawlow laboratory by Samojloff showed that the "digestion of the proteid columns" was "directly proportional to the length of the period of digestion."

Other researches by Borrisow established the rule that "the quantity of pepsin in the compared fluids is proportional to the square of the rapidity of digestion, *i. e.*, to the square of the column (expressed in millimeters) which the juices are capable of digesting in the same period of time." Schuetz (*Zeits. f. physiol. Chemie*, 1885, p. 577) had previously established this law for peptic activity by other methods. As Samojloff (*Archiv. des Sciences Biol.*, tome ii, St. Petersburg, 1893) has shown, this is not true, even for pure gastric juice, in concentrated solutions. It is still less true for concentrated chyme.

We will not attempt to describe all the modifications in technique that have been proposed by the numerous workers who have employed this method, though we have availed ourselves of such as proved useful. It will be necessary to refer to the work of Linoissier (*loc. cit.*) and of Nierenstein and Schiff (*loc. cit.*), since they introduced modifications in the test which are essential to adapt it to clinical use. The French writer described a method embodying the necessary changes, but it was left for the German authors to simplify and popularize these alterations. The latter consist, first, in a dilution of the stomach contents with a weak HCl solution to overcome the inhibition present in the concentrated chyme, to equalize the acidity, and to prevent too great a depth of digestion; and, second, in a corresponding prolongation of the period of digestion. Nierenstein and Schiff attribute the low results found in concentrated chyme to inhibition due to digested products (particularly carbohydrates) in solution. That this cannot be the sole reason is shown by Samojloff's work with pure gastric juice, quoted above. Danilewski and others have adduced evidence of a specific antipepsin. We will now describe the technique of the test somewhat minutely.

For filling the tubes we employ the whites of two or three eggs, well mixed to render the fluid as homogeneous as possible. Onuf (*Journal of the American Medical Association*, February 10, 1906) dries and re-dissolves the egg albumen, but this does not seem necessary to us, as we have been struck with the uniform results obtained with different lots of albumen. Thick-walled tubes of a caliber of 1 to 1.5 mm. are preferable to those of thinner walls and larger caliber, as they fracture more accurately, and yield more uniform albumen columns. Sections of tubing, suited in length to the vessel to be employed in boiling, are filled with fluid and egg-white by uction, and plugged with little balls of bread. When a sufficient number of tubes has been prepared they are dropped into a pan containing warm water, which is rapidly brought to the boiling point. This temperature should be maintained for five minutes, the tubes being meanwhile kept in constant motion. Violent ebullition is to be avoided as it may cause the formation of bubbles in the albumen, or expel the latter altogether. The use of the boiling temperature simplifies the test without greatly impairing its accuracy (Sahli, *Diagnosis*, Philadelphia, 1905). After drying, the tubes are hermetically sealed with sealing wax or paraffin, and allowed to ripen for several days. Fine bubbles, which are seen at first, gradually disappear, and the tubes remain in good condition for a long time, being practically sterile. When needed for use these tube lengths are cut into sections 2 to 3 centimeters in length, with a triangular file; accurate fraction of both glass and egg-white is the rule. Portions showing retraction of the albumen or bubbles are rejected.

For ordinary routine estimations we employ the undiluted gastric contents (15 c.c. or less), a dilution of one-fourth (4 c.c. to 12 c.c.), and a dilution of one-sixteenth (1 c.c. of contents to 15 c.c. of one-twentieth normal HCl). The latter dilution is the one used for quantitative comparisons. Two Mett tubes are placed in each dish, covered Stender dishes are most convenient, and the specimens allowed to digest in the incubator (37° C,) for twenty-four hours. At the end of this period the digested cylinders of egg albumen at each of the four ends are measured off, and the average reading calculated for each specimen. The relative amount of pepsin is then obtained by squaring the result, and if desired, multiplying by the dilution, *e. g.*, by 16. By using Cowie's table of squares (*Physician and Surgeon*, vol. xxvi, 1904) even this mild mathematical exercise may be avoided. For making the measurements a pair of calipers with a vernier reading 0.1 of a mm. is very convenient. A lens is useful principally for reading the vernier. One end of the tube is placed against one jaw of the instrument, and then the other jaw is separated until its edge is just visible through the opalescent edge of the albumen. If the tube is at all oblique the shortest side is taken, while if the albumen is uneven the highest point to which digestion has reached is measured. Air bubbles or separation of the albumen may lead to diminished or increased digestion, but the cause is usually evident.

To ascertain to what extent slight variations in the technique, such as are unavoidable in the ordinary clinical laboratory, affect the results of the test, we made several series of estimations, varying the conditions of the experiment in each case.

1. *Differences in the Caliber of the Tubes.* Pawlow states "that the diameter of the tube, even within wide limits, is without importance." Our tubes, with the exception noted below, were all within the usual limits, 1 to 2 mm. In the following series of twenty estimations a relatively large and relatively narrow tube were placed in each test mixture. As will be seen by the table the differences between opposite ends of the same tube are equally as great as

between tubes of different caliber. The greatest difference between any two readings was 0.6 mm.; the greatest difference between any reading and the average of four readings was only 0.4 mm. This demonstrates not only the unimportance of the exact size of the tubes, but also the accuracy of the readings in any given case.

TABLE I.

	Large caliber tube.		*Small caliber tube.*		
No.	Max.	Min.	Max.	Min.	Average.
1.	3.2 mm.	3.0 mm.	3.2 mm.	3.2 mm.	3.28
2.	2.8 “	2.8 “	2.8 “	2.8 “	2.8
3.	1.4 “	1.3 “	1.6 “	1.5 “	1.5
4.	2.4 “	2.4 “	3.0 “	2.4 “	2.6
5.	3.0 “	2.4 “	2.9 “	2.6 “	2.7
6.	2.1 “	1.9 “	1.9 “	1.9 “	2.0
7.	2.7 “	2.5 “	2.2 “	2.5 “	2.5
8.	2.7 “	2.7 “	2.7 “	2.5 “	2.7
9.	2.9 “	2.9 “	3.0 “	2.9 “	2.9
10	3.0 “	2.8 “	2.8 “	2.7 “	2.8
11.	3.3 “	3.2 “	3.3 “	3.1 “	3.2
12.	1.0 “	0.9 “	0.8 “	0.8 “	0.9
13.	1.0 “	1.0 “	1.4 “	1.2 “	1.2
14.	1.2 “	1.1 “	1.4 “	1.2 “	1.2
15.	1.4 “	1.3 “	1.4 “	1.0 “	1.3
16.	1.3 “	1.3 “	1.7 “	1.6 “	1.5
17.	3.5 “	3.4 “	3.5 “	3.3 “	3.4
18.	2.0 “	1.9 “	2.0 “	1.9 “	2.0
19.	2.0 “	1.8 “	2.0 “	1.9 “	1.9
20.	1.0 “	1.1 “	1.0 “	1.0 “	1.0

In a second series of tests the caliber of the larger tubes exceeded 2 mm. In each case there seems to have been uniformly greater digestion in the large caliber tubes.

TABLE II.

	Large caliber tube.		*Small caliber tube.*	
No.	Max.	Min.	Max.	Min.
21.	4.7 mm.	4.5 mm.	3.3 mm.	3.3 mm.
22.	3.4 “	3.1 “	2.4 “	2.3 “
23.	2.5 “	2.5 “	1.7 “	1.8 “
24.	2.4 “	2.4 “	2.0 “	2.0 “

2. *The Age of the Tubes.* Provided there is no separation of the albumen, nor putrefactive softening, age does not seem to affect the tubes. The method of preparation tends to make them sterile.

Tubes that are too fresh (less than 3 or 4 days old) are said to digest more rapidly than those that are "ripe."

TABLE III.—Table of tests to determine the effect of age on the degree of digestion. Mett tubes, varying in age from five months to four days: 0.5 per cent. pepsin solution in 1/20 normal HCl solution. Time, thirteen hours.

No.	Average.	No. tubes.	Readings.	Remarks.
1 (oldest).	6.5 mm.	3	6	Five months old.
2.	5.3 "	4	8	Several months old.
3.	6.4 "	3	6	Several weeks old.
4.	8.5 "	1	2	Nos. 4 to 6, four days old.
5.	6.3 "	3	6	Same heated for longer period.
6.	6. "	2	4	Prepared as No. 5; different egg.

It will be noted that in four of the six tests in the last table, including tubes varying in age from five months to four days, the results were quite uniform. In test four, another factor enters in, for in this case a lower degree of heat (80°) was used for coagulating the albumen, evidently insufficient. In five and six the heat was also low, but was continued for ten minutes. This shows that the degree of heat and its duration are important. Owing to the difficulty of keeping the temperature at 90° as originally recommended, it is better always to boil for five minutes.

The following table adapted from Linoissier shows the effect of variations in the time and temperature used for coagulation:

TABLE IV.

Temperature.	Time.	Digestion.
80° C.	1 minute.	17.40 mm.
" "	5 "	15.75 "
90° "	1 "	12.75 "
" "	5 "	10.30 "
100° "	1 "	11.10 "
" "	5 "	10.00

3. *Variations in Digestibility of Albumen from Different Eggs.* This is unimportant, as Table III incidentally shows.

4. *Variations in the Time of Digestion.* The degree of digestion, within certain limits, is said to vary directly with the time of digestion. Pawlow stated this to be true for ten hours. Nierenstein and Schiff, in diluted contents, found it true for twenty-four hours. So also have Linoissier, Cowie, and others. We believe this to be true,

though the only series of tests we made did not support this view. In the series of eight tests, shown in Table V, the tubes were read at thirteen and twenty-one hours. In each case the second reading was less than it theoretically should have been. As our incubator was rather erratic in its temperature, we cannot reverse previous results on the strength of this experiment.

TABLE V.—Average Readings.

No.	13 hours.	21 hours.	Theoretical.
1.	6.5	7.4	9.8
2.	5.3	5.8	7.8
3.	6.4	7.5	9.6
4.	8.5	9.5	12.7
5.	6.3	6.7	9.4
6.	6.0	6.2	9.0
7.	7.1	7.5	10.6
8.	6.3	6.6	9.4

(Eight other tests showed similar results.)

5. *Variations in the Temperature of the Incubator.* This is undoubtedly of importance, but we have no data to offer.

The effect of variations in the original acidity of the gastric contents have been provided against in the technique of the method. The effect of inhibitory factors was studied by Nierenstein and Schiff. Our experiments in this line are described in detail elsewhere.

On the whole, therefore, we have in Mett's method, as modified by Nierenstein and Schiff, a sufficiently accurate measure of the activity of pepsin. Owing to the nature of pepsin, and the complex character of the inhibitory factors, very exact comparative estimations are not to be expected. With careful technique, however, the test is found to be surprisingly accurate in any given case. When the inhibitory factors are better understood it will be still more available, and itself offers the best means of unravelling the tangle. As a qualitative or, roughly, a quantitative method it also has much to recommend it, since the tubes are easy to prepare, and may be more readily preserved than the customary disks of egg albumen. We have made between 400 and 500 tests, partly experimental and partly clinical, and are well satisfied with the results, some of which will be published shortly. *June* 14, 1906.

Thrombosis of the Superior Mesenteric Artery with Hemorrhagic Infarction and Perforation of the Ileum.

By JOHN FUNKE, M.D.

(From the Laboratories of the Jefferson Medical College Hospital.)

This paper is based upon the results of an autopsy in which, among other lesions, a purulent inflammation of the peritoneum consecutive to a perforation of the ileum was found. The clinical diagnosis of the case was intestinal obstruction.

The right iliac fossa contained 30 c.c. of grayish-yellow purulent fluid and a considerable amount of intestinal contents: the peritoneum in this area was reddened at points, at other places it was covered with masses of fibrin agglutinating the coils of the intestines. The condition, while most advanced in the area named, also extended toward the other side and into the pelvis. As the coils of intestine were separated, about 1 meter from the ileocecal valve a small irregular opening was found in the ileum, from which the intestinal contents oozed. When the intestines were opened the area in which the perforation had taken place did not contain a Peyer patch. Its long axis ran transversely to the long axis of the bowel. The margin of the area was elevated, reddened, denser than the surrounding structure and appeared undermined. The ulcer was oval in outline, the floor red and ragged; the perforation occurred near the center; its margin was irregular, fragmented and measured 0.5 by 1 cm. in diameter. At a point 10 cm. toward the ileo-cecal valve was another ulcer which apparently had been formed by coalescence of two smaller necrotic areas; the ulcer measured 2 by 3 cm. In structure it was similar to the other except there was no perforation. The mucosa of the ileum was slightly thickened, edematous, and covered with tenacious mucoid substance. The solitary and aggregated follicles were moderately swollen. The duodenum and jejunum presented nothing noteworthy but the catarrhal condition of the mucosa of the colon was pronounced.

The heart showed a moderate amount of fibroid degeneration but the valve leaflets were little altered.

The bronchi contained fecal matter; there was no evidence of a beginning pneumonia.

The larger vessels were moderately sclerotic; the superior mesenteric artery contained neither a thrombus nor an embolus, nor was it in any way diseased so far as could be determined with the naked eye. Unfortunately the portal vein was not examined so that thrombosis of that structure cannot be excluded, although the mesenteric and branches of the portal vein were not distended. The inferior mesenteric artery was not opened since, because of its distribution, it is not likely that the infarcts could have resulted from an embolus or a thrombus of that structure.

Histologically the mucosa of the sections made from one of the ulcers described is greatly altered; the floor of the ulcer is made up of necrotic material which contains many cells, principally leukocytes, red blood cells, and fibrin. Near the normal tissue, but still in the necrotic mass, there is an abundant infiltration of blood. This hemorrhage is not confined to the necrotic tissue but is also found in the submucosa, serosa, and to a certain extent in the musculature. The submucosa contains many bloodvessels which are thrombosed and in the thrombi are many endothelial cells. The mucosa forming the margin of the ulcer is necrotic at points, the condition being most marked between the valvulæ conniventes, especially if the tips of these structures lie in contact, forming an enclosure which is poorly drained. The necrosis in these areas involves generally the whole mucosa. The epithelum of the crypts near the surface of the mucosa is necrotic while those cells in the deeper portion of the tubules are as a rule fairly well preserved. The interstitial tissue is abundantly infiltrated with formative cells, including a few leukocytes; there is also present some newly formed fibrous tissue. The interstitial inflammation is evidently older and in all probability existed for some time before the ulcers were formed. Occasionally extravasations of blood are found in this part of the mucosa, but are more abundant in the submucosa, which structure is involved to a greater extent than the remaining coats.

Anatomical Diagnosis. Chronic adherent pleurisy; chronic myocarditis; chronic interstitial nephritis; chronic catarrhal ileocolitis; acute purulent peritonitis with perforation of intestine; hemorrhagic infarction of the ileum.

In regard to the etiological factors in thrombosis and embolism of the superior mesenteric artery, a study of the recorded observations shows that arteriosclerosis is present in most cases, and that endocarditis is the next most frequent accompanying lesion. Virchow found at autopsy vegetations on the tricuspid valves, a thrombus in the left auricle, stenosis of the mitral, and vegetations on the aortic leaflets. The case observed by Kaufmann and the one recorded by Scott showed thrombosis of the left auricle. Reitter reported a case in which mitral stenosis and regurgitation were present. Similar cases are recorded by Osler and also by Claisse and Abrami. Beckmann found calcareous patches in the aorta and he believed the embolus in the superior mesenteric artery was a detached fragment of the vessel wall. Kussmann's case showed an acute endocarditis of the mitral valve and infarction of both kidneys. Deckart records a similar case. In Oppolzer's case, mitral stenosis, in which the surface of the valves was smooth, atheroma of the aorta and hemorrhagic gastric erosions consecutive to gastric catarrh were found. He is inclined to believe that the clot in the superior mesenteric artery arose from a thrombus in the heart, although upon this point there is no conclusive evidence. Faber, in one of his cases, holds the endocarditis responsible for the embolus; the second he attributes to an aortic thrombus; while in the third he is somewhat in doubt as to whether the thrombus in the left ventricle or the endocarditis should be incriminated; in the fourth case the cause could not be determined. E. Grawitz observed in one of his cases a chronic interstitial nephritis, hypertrophy, and dilatation of the heart, a dissecting aneurysm of the aorta, atheroma of the larger vessels, infarction of the spleen, circumscribed peritonitis, catarrhal pneumonia, and cerebral apoplexy. He believes all the conditions present can be traced to the changes in the kidneys, which first induced the alterations in the heart; these in turn gave rise to the atheroma which was responsible for the emboli. In another case, he attributes the condition to changes in the spleen incident to malaria. The cause of the thrombosis in the two cases reported by Moyes was disease of the mitral valve, upon which, in each case, he found a roughened area. Foulis reported a similar case. Bradford attributed the thrombus in the superior mesenteric vein to disease of the mesenteric lymph nodes, for which disease he could find no cause. The valve leaflets of the aorta and the branches of this vessel were normal in Litten's case, and there was no thrombus in the cavities of the heart; the mesenteric artery was occluded by a thrombus, which he attributes to a circumscribed endarteritis. Lorenz reports a case which presented a condition very much like the last. A similar case was recorded by Firket and Malvoz, but Nothnagel maintains that in this case it cannot be settled beyond doubt that the thrombus was spontaneous, since in addition to the atheroma of the mesenteric vessels there was a widespread atheroma of the aorta and endocardium. In Nothnagel's case there were capillary emboli in the arteries of the intestinal wall. The emboli were consecutive to pulmonary abscess. This patient had been in the habit of injecting morphine into his arm for years; the skin was covered with ulcers and the axillary lymph nodes were suppurating; the patient died with symptoms of pyemia. Mall states that when the splanchnic nerves are irritated the mesenteric vessels contract. Pilliet has been struck by the obesity of his two patients, and suggests that possibly this condition is instrumental in bringing about venous stasis. He holds that the thrombosis is ascending and comes from the intestines, and is of an infectious or toxic nature. It is difficult, he notes, to establish that the micro-organisms found in the glands are primarily the cause of the affection, for they may have developed on the gangrenous mucosa after the thrombosis. In Cramer's case the occlusion of the artery occurred eleven days after confinement. Although no clinical data point to the existence of a puerperal septic endocarditis and no autopsy was obtained, he suggests that during the puerperium an endocarditis may have instituted a warty-like growth on the valves instead of an ulcerative process and produced no symptoms. He carries his speculation a step farther and supposes that the embolus arose from a venous thrombosis of the puerperium, but instead of passing through the pulmonary circulation it entered the left auricle through the foramen ovale. As causes of thrombosis or embolism of the superior mesenteric artery, Welch mentions thrombus in the left heart, atheroma or aneurysm of the aorta, and thrombus in the pulmonary veins caused by gangrene of the lung.

The cause of the hemorrhagic infarction in the case reported in this paper is evidently obscure, since there was no heart lesion and the arteriosclerosis appeared insufficient to explain the phenomena. Yet from the character of the lesion found one would not suspect a thrombus or an embolus in the trunk or even in the larger branches of the artery. From the histological picture I am inclined to think that the catarrhal inflammation which had been present for some time instituted the evident thrombosis of the finer branches.

Schloffer by experimental investigation found that if the mesenteric vessels were divided at a point less than 2 cm. from the intestinal wall ulceration did not occur, but if the division were at a point more than 5 cm. from the intestinal wall perforation and fatal peritonitis ensued, and if the division were between these two points ulceration always occurred, which, however, healed and produced a stricture.

The extent of the lesion resulting from the obstruction of the superior mesenteric artery depends entirely upon the site of the occlusion. If, as observed by Virchow, Beckmann, Taydor, Moyes, Kussmann, Oppolzer, Eisenlohr, Claisse and Abrami, Kaufmann, Deckart, Gordon, Munro, Cramer, Conti, Cattani, Councilman, and also Leclere and Beutter, the occluding body is in the main trunk of the superior mesenteric artery, the mucosa of the lower portion of the duodenum, the whole jejunum, ileum, and ascending colon are swollen red or reddish black and brittle. Occasionally a portion of the mucosa is separated and is necrotic. In many instances the lumen of the intestine contains considerable blood. Hemorrhage is occasionally seen in the mesentery. The presence of hemorrhagic infarction followed by ulceration has been noted by Councilman, Reitter, Lohr, Parenski, Lorenz, and also Firket and Malvoz. Conti observed a case terminating in perforation of the transverse colon, followed by general peritonitis. Kaufmann also noted a perforation in one case, but he believes it was artificial. Watson, Pieper, Ponfick, Elliott, and Lothrop report cases of embolism of the superior mesenteric artery with general peritonitis, but no perforation. Howse records one case in which fistulous communication existed between the coils of the intestine.

Finlayson, Moos, Cohen, Karcher, Virchow, and Chiene report cases of embolism of the superior mesenteric artery which recovered.

Considerable experimental work has been done with the view of determining the route by which the blood reaches the interstitial structure of the intestinal wall after the occlusion of the artery. Deckart attributes to Cohnheim the statement that infarction of the mucosa of the intestine does not occur unless there are emboli or thrombi in the smaller branches of the mesenteric artery as well as in the trunk or in the larger branches. Litten found when the artery of an animal was ligated, hemorrhagic and suppurative peritonitis developed and the mesenteric lymph nodes and Peyer's patches became swollen. The lower portion of the duodenum, the jejunum, the ileum, and the ascending colon were reddened and the mucosa edematous. If a comparatively large branch was ligated, hemorrhagic infarction developed. He ligated the trunk of the superior mesenteric artery and observed the changes in the intestines until death of the animal ensued. The wound of the abdomen was closed with clamps, so that he could at any time draw out the intestines. The intestines at first became pale, nodular, and contracted; the arteries collapsed and the veins became distended. Soon the intestines relaxed and became dilated. Since the circulation was not re-established, he declares that the influx of blood must be, as pointed out by Cohnheim, through venous regurgitation. By experimental observation Litten determined that the walls of the capillaries and the small veins undergo necrosis in from two to two and a half hours after the circulation ceases. He then found that when the superior mesenteric artery is ligated and a solution of indigo is injected into the jugular vein, the area supplied by the occluded artery remains uncolored, while the rest of the body is tinged blue. The same results are obtained if the solution is injected into the left heart. He concludes from his experiments that the superior mesenteric artery is functionally an end artery. Contrary to the views expressed by Litten, Cohen holds that venous regurgitation is not responsible for the hemorrhagic infarction, but that the blood is brought to the parts by the collateral circulation; when the mesenteric vein is ligated the area becomes infiltrated with more blood than if the artery alone had been occluded. Cohen's view is contradicted by Faber, who maintains that the vascular area of the superior mesenteric artery is too large, the inferior mesenteric cannot furnish enough blood to raise the pressure in the affected part to any appreciable degree. Then, too, the escape of the blood from the inferior artery into the veins is easier than its escape into the superior mesenteric artery. Therefore, he believes that after occlusion of the superior mesenteric artery the pressure within the vessel falls to zero, and since it is positive in the portal vein, regurgitation occurs. By ligating the left renal vein and the superior mesenteric artery in animals he produced lesions similar to those seen in man after occlusion of the artery. He then ligated the superior mesenteric artery and the branch of the portal vein that enters the left lobe of the liver. Five hours after the operation he killed the animal and found the lower portion of the duodenum, the jejunum, and part of the ileum injected, but not the lower fourth of the small intestines. Mall tells us that immediately after the closure of the main trunk of the superior mesenteric artery the intestines of an animal experimented upon are thrown into violent contraction; they remain anemic and contracted for two or three hours, when the spasm relaxes and the ischemia gives way to venous engorgement and infarction. The intestinal contraction, which, under the circumstances, is equivalent to the arterial spasm, is probably one, although not the sole reason why, in spite of the free anastomosis, occlusion of the artery supplying the intestine is followed by necrosis and infarction. Hemmeter maintains that the whole vascular area of the superior mesenteric artery can be injected from the aorta after the main trunk has been ligated, but in the living being and in animals the different conditions of pressure control the distribution of the circulation blood. The pressure, which is reduced to zero when the blood supply is cut off, cannot be raised by the inflowing blood from the inferior mesenteric artery, for the amount is too small. Although infarction occurred after Cohen ligated the mesenteric vein, I am inclined to think the anastomosis of the veins is even greater than that of the arteries, so that the blood from the portal vein, which has a positive pressure, will find its way into the anemic area, even though the mesenteric vein is ligated.

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The Mechanism of Resistance to Tuberculosis.

ADDRESS AT THE ANNUAL CONVERSATIONAL MEETING (APRIL 26, 1906).

By EDWARD R. BALDWIN, M.D.,
SARANAC LAKE, N. Y.

Mr. Chairman, Ladies and Gentlemen: In these remarks it is not my purpose to discuss the entire subject of resistance against this disease, including, as it should, external measures—hygiene, diet, etc.—when used in a broad sense; but rather the present state of our knowledge of the biological aspect, the vital resisting weapons of the animal body and their phenomena in relation to tuberculous infection.

Neither do I invite your attention to every phase of this aspect of the subject, for it would indeed be an ambitious task to attempt an explanation of all the mechanisms, and I shall submit only such deductions as have seemed to be warranted by accumulated facts and analogies with other diseases.

We have eagerly snatched hints from every field of biological research to aid us in the interpretation of these mysteries in connection with each disease, and in none more than tuberculosis; for the difficulties involved in experimentation with it, and yet more in the interpretation thereof, are unusual, disconcerting, and often harassing.

In the immunity studies of late years in connection with other disease agents, much aid has come to the student of tuberculosis; for the laws of tissue reactions, and defensive mechanisms in animals, have been found quite generally applicable to pathogenic bacteria. The receptor apparatus, for the purpose of antitoxic, agglutinative, bacteriolytic or digestive activity and the phagocytic powers, are called into operation in greater or less degree with each kind of infection, according to its individual form of attack, and vulnerability to the defenses. It is war in a microscopic world and the whole subject lends itself readily to this metaphorical description, from which temptation one must refrain, by reason of the danger that warped and half-proved conceptions may easily lead astray.

APPLICATION OF GENERAL DEFENSIVE POWERS TO TUBERCULOSIS. What then do we know about the general methods of defense employed against the tubercle bacillus by animal organisms? How do they differ from those directed against other diseases?

In approaching the subject we may do well to consider—first, the peculiarities of the parasite itself; second, the course of infection in animals with normal resistance; third, with lessened resistance; fourth, with increased resistance, and, finally, the explanations ventured for the reactive phenomena, and their coincidence or harmony with clinical observations and empirical therapeutic measures.

PECULIAR CHARACTERISTICS OF THE TUBERCLE BACILLUS. It is well known that the tubercle bacillus is something more than a bacterium; it is an intermediate organism between bacteria and a higher order of plants known as hyphomyces and they have been called tuberculomyces for the sake of greater accuracy. While this fungus-like character is less marked in proportion to their greater parasitic power, it doubtless accounts for their slow multiplication and high resistance to disintegration as compared with the lower bacteria. From the biochemic standpoint it is distinguished not only by an insignificant secretion of soluble toxin but by an incredibly resistant endotoxin. This is a nuclein substance in combination with a complex wax to which is due the high acid resistance after staining. The decomposition of this nuclein sets free a special nucleic acid which is the essence of its toxic activity, and it is important to bear in mind the foregoing facts to understand the obvious difficulty encountered by the animal tissues in disposing of tubercle bacilli by the usual bacteriolytic powers. Even the dead bacilli require nearly the same effort on the part of the body to disintegrate and digest them as foreign dead matter, and the tissues often suffer irreparable harm from their poison. It has been mooted that tubercle bacilli and some other bacteria produce different toxins during their parasitic growth from those detected in artificial cultures. It is hardly possible that such can exceed in importance the endotoxin to which practically all the symptoms in the course of this disease are referable. The small amount of toxin that is set free in the lifetime of the bacillus in cultures is apparently (except for a minute amount of fatty acid), of the same nucleoproteid nature as that of the bacillus body itself, though more soluble and less intimately combined with the wax. On the other hand, that there is some difference between the living and dead bacilli—possibly attributable to some secretion during life—is suggested by the greater protection conferred by the living as compared with the dead bacillus in immunization experiments; this is, however, by no means ascertained.

On the part of the bacillus we have also to consider its virulence and origin, whether from human, bovine, or avian source, for the results of inoculations are somewhat varied from these causes. The differences in virulence are not understood though various explanations have been offered. Prof. Welch's[1] theory of the adaptation of bacteria to parasitism by the production of new receptors has been supported by Theobald Smith[2] in connection with tubercle bacilli.* Differences in toxic strength have not been clearly associated with alterations of virulence, except as between the different races of bacilli, and those altered by prolonged cultivation. It has, however, been shown that the substance of the human bacilli varies in toxicity and that of the bovine is more poisonous to guinea-pigs. Of a specific "aggressin" or "aggressiveness" in connection with the virulence of tubercle bacilli, I will speak later.

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* Since this address was given Prof. Smith has again reiterated his belief in the special secretion theory. Jour. Amer. Med. Assoc., April 28, 1906.

RESISTANCE OF NORMAL ANIMALS TO INOCULATION. We next turn to the investigation of the response made by animals possessed of their normal resistance to artificial or natural infection with tuberculosis. In doing this we must distinguish between individuals who have had a previous tuberculous infection, for a marked difference may result in the reaction. The importance of this is at present being urged by v. Behring[3] in connection with his novel ideas as to predisposition and immunity; I shall also return to this subject again.

The reaction to an artificial infection for the first time with a moderate number of bacilli of average virulence differs but slightly in form whether they are introduced under the skin, into a serous cavity, or directly into the blood stream. There are, nevertheless, considerable differences in the intensity of the phenomena and the time during which they develop.

SUBCUTANEOUS INFECTION. At the site of subcutaneous inoculation there is at once an emigration of polynuclear leukocytes which begin to phagocyte the bacilli. This is not accomplished so completely that all the bacilli will be found englobed, though some may escape from phagocytes after having been thus taken in, the latter having suffered harm in performing their function. Such injured phagocytes show unmistakable degenerative changes (vacuoles and fragmented nuclei). Some of the bacilli both within and outside of the phagocytes soon exhibit lysis, inasmuch as they lose their regular contour and become vacuolated. There is also a small lymphocyte collection and serous exudate, but these cells rarely participate in the phagocytosis. After three or four days, however, large mononuclear cells (macrophages) appear and continue the phagocytosis both of the bacilli and dead polynuclears. Accompanying this stage and while the local reaction is apparently subsiding the lymph passages have permitted bacilli to pass to the regional lymph nodes, whether solely carried free by the lymph stream or with the aid of leukocytes is uncertain. The behavior of lymph nodes at this juncture is a matter which has lately received fresh attention in connection with the studies on the channels of infection in tuberculosis and its latency, and appears to be of paramount interest.

Ten years ago the Italians, Manfredi,[6] Perez and Viola, claimed that tubercle bacilli (as also other infections), remained latent in lymph nodes for undetermined periods of time without exciting visible changes in this tissue, but with gradual loss of virulence, phagocytosis being absent. These observations have been confirmed in some respects by v. Behring,[3] Weleminsky,[7] Bartel and Neumann,[9] Harbitz,[10] Rosenberger[8] and others. The latent period during which the bacilli do not appear to multiply nor the nodes to indicate noticeable hyperplasia is from ten to twelve days after experimental infection. From this time forward both the point of inoculation and regional nodes become infiltrated with leukocytes and there is connective-tissue proliferation, epitheloid and giant-cell formation if the resistance is good, or caseation with gradual destruction if the disease progresses. The local swelling and enlargement of neighboring nodes is greater the less the virulence of the inoculated tubercle bacilli. The general reaction also begins to manifest itself after ten to twelve days by the phenomenon of tuberculin susceptibility. Febrile disturbance and more or less specific agglutinins and so-called opsonins develop in the serum, indicating the entrance of bacilli or their products into the blood stream with the resultant reactions which lead to the formation of anti-bodies. General leukocytosis is absent or very slight, though according to Arneth[11] characteristic changes occur in the number and shape of the nuclei in the polynuclear neutrophiles. Those containing four or more nuclei are lessened, and this is ascribed to the death of the phagocytes employed in defense. When the serous cavities are infected there is more play for the leukocyte reactions, more rapid transitions and quicker spread or death of the bacilli. Likewise after inoculation into the blood stream the polynuclears rapidly gather about the bacilli at their point of lodgement, and are replaced later by a cordon of lymphocytes and proliferated endothelia with the further stages of miliary tuberculosis.

NATURAL INFECTION. The course of natural infection and its resistance is at present a timely subject, but we are concerned only with the forces that combat it; and particularly with the differences which obtain in the reaction between the cutaneous and mucous membrane pathway at the point of entrance.

As is well known the integument is quite resistant during healthy adult life in man and the bacillus ordinarily finds the local resistance in the form of cell reactions an effective barrier. (Lupus is, of course, an exception which requires separate consideration.) It is, however, otherwise with infants and some of the lower animals, *e. g.*, the simians, in whom general infection usually takes place from abraded skin surfaces. So far as I can ascertain, no evidence exists that such infections occur without signs of reaction at the site of inoculation at some stage of the disease. On the other hand, it seems proved beyond doubt that bacilli can pass through or between the epithelium of lymph follicles and mucosa into the lymph nodes, both in infancy and in adult life, without leaving traces of their point of entrance. Notable contributions on this subject have been made by Ravenel,[12] Walsham,[13] Weleminsky,[7] v. Behring and Roemer[3] and many others, and the problem is today one of especial importance. The new conceptions of tuberculous infection, predisposition and immunity which have been promulgated by v. Behring[3] relate principally to the character of the response made by the lymphoid tissue to the primary infection by tubercle bacilli, and demand careful attention, however cautiously we may adopt his conclusions. When virulent bacilli find lodgement in the lymph nodes for the first time in considerable numbers it is evident from experiment that infection is likely to occur, but such combinations do not invariably happen under natural conditions, and the protective mechanism is able to dispose of a certain number of weaker bacilli in the lymph nodes or blood stream with or without persistent or manifest histological changes. It seems apparent from whatever site the bacillus may gain access to the lymph spaces in natural conditions, whether from the respiratory or alimentary mucosa, the resisting mechanism of the lymph nodes chiefly determines its fate and is of prime importance. Even when tubercles are formed in the nodes, it has long been observed that few bacilli can be found in them as compared with foci elsewhere. It has also been held that their virulence is less, but this is probably a temporary characteristic and is contradicted by the experiments of Krompecher and Zimmerman,[15] who compared cultures from the lung and lymph nodes. The fragmented and poorly stained bacilli frequently found in nodes are certainly further evidence of the lymphatic resisting power, though the wandering phagocytes may have participated at first in their destruction. I have yet to mention the resistance offered in the alveoli of the lung to inhaled bacilli. As it is at present one of the disputed questions whether primary infection often occurs through the epithelial layers of the alveoli, we are only safe in saying that these surfaces appear vulnerable to secondary infection.

To sum up briefly: the normal resistance to lymphatic infection by tubercle bacilli presents phenomena of phagocytosis, at first polynuclear, then large mononuclear; connective tissue proliferation; a stage of latency and absence of constitutional symptoms, during which time the bacilli may be found in the lymph nodes and site of inoculation (if artificial); evidence of lysis of the bacilli; a stage of constitutional and local reaction denoted by fever or tuberculin susceptibility, and the appearance of agglutinins and other anti-bodies in the serum. Finally, hyperplasia of the regional lymph nodes, recovery, latency, or further spread of the infection with caseous destruction takes place. It must not be thought that this describes all the changes and possible variations, but I conceive these most important for the elucidation of the problem in the narrow sense first indicated.

LOWERED RESISTANCE. In the observations which will next be made on the signs of lowered resistance we should expect to obtain some hints—by way of contrast with the normal—toward explaining the mechanism of resistance; this is probably true but less obvious than from the indications of increased resistance.

To return to the course of infection after subcutaneous inoculation, we note at once much weaker phagocytosis, though I am not aware that studies have been made under these conditions on that point; it is true, nevertheless, for the peritoneum. What is of equal significance, however, is the markedly less infiltration at the site of inoculation and much less hyperplasia of the lymph nodes. Polynuclears are few, lymphocytes predominate in the exudate, and numerous fragmented nuclei appear; caseous changes rapidly supervene in the nodes with evidence of growth of the bacilli. Constitutional disturbance begins at once with fever, wasting and weakness; none or very little agglutinin and opsonin is discoverable in the serum. Sometimes the tendency to formation of tubercle is so feeble that the bacilli, when introduced into the blood stream, cause a true septicemia by multiplying in the blood itself. This was first described by Yersin, 1888,[14] in connection with chicken tuberculosis inoculated into rabbits, and was observed by Roemer,[4] Weber and Bofinger[16] in mice. On the other hand, under some conditions of defective resistance in animals and man, the infection produces grave toxemia without noticeable growth of bacilli and tubercle formation. In these cases phagocytosis and local inflammation are practically absent, but there can be little doubt that bacteriolysis takes place with resulting cachectic poisoning from the toxic products, and unfavorable conditions for further proliferation of the bacillus. These contradictory conditions have analogies in other diseases for which explanations have been forthcoming of late.

From what has been said, therefore, it appears that lowered resistance to tuberculosis is indicated by weakened phagocytosis, or bacteriolysis with normal toxin susceptibility; or it may mean the anomaly of normal, or exaggerated bacteriolysis with great toxin susceptibility. Further, the description above given applies to the course of virulent infection in the presence of normal resistance.

HEIGHTENED RESISTANCE OR IMMUNITY. Let us now examine the manifestations of heightened resistance to tuberculosis, which, for practical purposes, means immunity to many individuals.

It is obvious from experiment and experience under natural conditions of life that bacilli, living and dead, must be received into the tissues and overcome occasionally, if not infrequently. It follows from biologic laws that successful adaptation to harmful agents gradually evolves greater general and even specific resisting power in the cell groups which have been exposed to such influences. Hence, in healthy adult life ample resistance to tuberculous infection might be anticipated, and far more had a series of exposures been previously overcome without resulting infection.

From what has already been said, it may be inferred that there is much in recent work on the pathways of infection to show that it is not so frequently through the pulmonary alveoli as formerly supposed, but that it passes into the lymphatic system from one of the many mucous surfaces. The lymphatic cells, then, should develop the heightened resisting power to cope with the bacillus. This, as I understand it, is the basis of v. Behring's theory of immunity to tuberculosis, when divested of explanatory details for which we await his proofs.

I deem it of sufficient importance at this point to mention his published ideas about the importance of primary infection of the lymph nodes and what occurs after complete or partial recovery (Leitsätze, 29–30, Beiträge, No. 8) without reference to the sources of infection. According to v. Behring, functional alterations in the lymphatic and vascular systems occur, which result in immunity on the one hand, or in the scrofulous diathesis on the other. He thinks that probably the muscular walls of the bloodvessels are the seat of changes, which, at least in the beginning, are expressed by hypersusceptibility to the bacillus poison.

This scrofulous diathesis is denoted by changes in the vascular and lymphatic systems that easily lead to caseous tubercle upon a renewed infection. A latent or manifest scrofulosis due to infantile infection constitutes, for v. Behring, the only specific "predisposition" to tuberculosis. I have presented these ideas thus fully that we may contemplate some of the evidences of increased resistance in this aspect, omitting v. Behring's explanations.

Koch[17] had first noted that a second infection during the course of tuberculosis in guinea-pigs was followed by a local reaction at the point of re-inoculation, but the regional lymph nodes escaped enlargement and the second infection remained localized; meantime the ulcer at the site of the first became healed. Similar observations were made by Trudeau, in 1890,[18] in rabbits' eyes under different conditions; also by Arloing[19] in 1903. More recently Weleminsky,[7] v. Behring,[3] and Roemer[5] have directed attention anew to the improbability of a second lymphatic infection in man because of the heightened resistance created by the first. The insusceptibility of the bronchial and intestinal mucosa to the presence of bacilli in the sputum of tuberculous persons—often for years, provided the general resistance is maintained—is cited as evidence of this auto-immunity of the lymphatic system. Furthermore, Roemer[5] relates attempts to immunize calves with intravenous inoculation of weak virulent bovine bacilli which produced a chronic disease and death at length. Although second inoculations of virulent bacilli were given subcutaneously to these animals he believes they failed to infect, the animal having succumbed to the original inoculation. Whatever importance these differences between primary and secondary infection may ultimately have, they are significant of specific changes in the animal organism along the lines of resistance. It cannot be denied, however, that many difficulties meet us in accounting for the origin and spread of natural infections which we have reason to believe are secondary. Neither is it easy to understand the contradiction involved in a theory of predisposition due to primary infantile infection which stamps a susceptibility to secondary infection on the tissues, while during the course of an actual progressive disease a relative immunity exists. Further, v. Behring believes that individuals who have become toxin-susceptible tend to tubercle formation at the site of subsequent infection; even lupus is ascribed to an additional infection in scrofulosis. Surely a persistent local ulcer is not easily conceived as a sign of resistance, yet we know from a clinical point of view that such conditions are associated with extremely mild or chronic types of tuberculosis. In contrast to the last-mentioned there are several other signs of heightened resistance in clinical observations which I will simply mention here: I refer to the subsidence of laryngeal infiltration and healing of ulcers in the same region during an exacerbation of the accompanying pulmonary disease; the healing of pulmonary ulcerations after an intercurrent attack of pleurisy with effusion or other intercurrent disease; the change in character from acute to chronic when a pulmonary lesion becomes disseminated, as, for example, during some hemoptyses. To these might be added the effect of therapeutic measures, surgical and otherwise, which, whether specific or not, result in changes favorable to the more or less successful combat on the part of the tissues against the bacillus. Nevertheless it must not be thought that the ultimate result of these manifestations of resistance to the bacillus is in all cases favorable to the tuberculous individual, for we have already noted that toxin susceptibility may exist in the presence of conditions that are inimical to the life of the bacillus; it may, indeed, even develop in consequence of their death, causing grave cachexia.

The most important evidence of the possibilities in the way of increasing resistance is, as you know, the immunization of cattle just now emerging from the experimental stage. While the honors in developing artificial immunization methods appear to go abroad, it may be a gratification to know that much groundwork was done in this country by de Schweinitz,[20] Trudeau,[18] Pearson and Gilliland,[21] and Theobald Smith.[2]

Previous to and during the tuberculin era, Courmont and Dor, Grancher and Martin, and Hericourt and Richet[22] had experimented with rather indifferent results, though today we know that marked resistance can be produced by similar inoculations of weak virulent bacilli, which they employed. Close attention of late years has been given to the nature of this protective mechanism and I well remember, as early as 1892, the reactions seen in rabbits' eyes, which were pointed out to me by Dr. Trudeau during his experiments with various immunization methods; and how we noted the striking difference in the reaction to the eye inoculations between the untreated animals and those previously treated with dead bacilli. In the controls no inflammation was apparent after the first traumatic irritation had subsided in the corneal wound, until the tenth or twelfth day, when the inflammation slowly returned and gradually destroyed the eye by caseation. The treated animals, on the other hand, had marked inflammation from the first, with evident swelling of the iris, and with conjunctival and corneal infiltration; but after ten to fifteen days a subsidence occurred with clearing of the cornea and eventual recovery without caseation when the conditions were all favorable as to the dose, etc.

The marked resemblance between these phenomena and tuberculin reactions is obvious to any one acquainted with the subject, but where the latter are intermittent, according to the excitations from the injections, the former are continuous, apparently until the bacilli are killed or rendered harmless. Microscopic appearances justify this opinion as do the ultimate results. Minute examination of this reaction in different stages was made by Dr. Joseph Nichols[23] in 1904, in connection with the lungs of vaccinated hares, and the conclusion was made that the process was an intense phagocytosis with lysis of the bacilli. While the local reaction is severe there is also a general leukocytosis, fever and increase of agglutinin in the serum. From what has been depicted of this reaction it is clear that this stage of specific resistance involves susceptibility of certain cells to the poison, which is more of the nature of excitation to successful digestion and absorption rather than death in consequence of its action. In calves, at least, a stage is attained after intravenous inoculations of human bacilli, when further inoculation of virulent human or bovine cultures in moderate amount produce no fever reaction beyond a trifling one on the day of inoculation. I do not know that anyone has shown that a local reaction is absent, but it is unaccompanied by serious disturbances due to the toxin from the digested and absorbed bacilli.

I have tried to sketch in the foregoing only types of successfully increased resistance, for complete immunity under severest experimental conditions is, to my knowledge at least, unattainable.

EXPLANATION OF RESISTANCE MECHANISM. We finally come to inquire what the nature of these various responses by the cells and fluids of the body really is. In the first place we are struck by the part which phagocytosis plays in the normal reaction and the tendency which is thus shown to localize the damage. Yet is it not so certain that the leukocytes do not wander away with their burden of bacilli and form, perchance, some new foci. It has not been shown that the bacilli die in the phagocytes, nor does the serum alone or in conjunction with the phagocytes apparently accomplish the death of all the bacilli. Yet, by analogy and from appearances, we must ascribe the bacteriolytic function to both agencies; only, because of the excessive refractoriness to digestion possessed by the bacillus, the process is slow and less easily observed.

The function of the lymphocytes and the parenchymatous cells of the lymph nodes is less definitely connected with the lytic power, but experiments already mentioned by Manfredi,[6] Blumreich and Jacoby,[24] v. Behring[3] and Bartel,[9] point to such a function in addition to a toxin-absorbing and toxin-digesting as one of the greatest importance. From v. Behring's recent announcement, though somewhat vague, it would seem that he had discovered such properties in the lymphatic tissue of immunized animals.

The important subject of the selective affinity of tuberculous toxin for special cell groups has but recently received attention, and, so far as I know, only by v. Behring. In his *Beitrag*, 1905, No. 10, pp. 4–6, he gave the provisional opinion that the leukocytes and smooth muscular fiber of the small arteries were the specially sensitive cells, because he conceives them to be associated with tuberculin hypersusceptibility with or without the presence of tubercles.

However this may be, we are able to note marked sensitiveness to tuberculin in the cells directly exposed to the influence of the poison and immediately around the tubercles, wherever situated.

The localization of the bacilli in the tubercles and the difficulties in the diffusion of its endotoxin, easily account for the paucity of antibodies in the general circulation. The presence of agglutinin is demonstrated hardly more in tuberculous than in normal serums unless the individuals are undergoing immunization treatment with the specific substance, when it may increase to a high degree and tend to localize bacilli which might otherwise spread in the blood.

I will only touch upon the much-disputed question about the possibility of an antitoxin to mention the generally negative results of experiments, so far as a direct neutralization of the toxin is concerned. Quite recently Karwacki[25] published some tests with the Maragliano serum and toxin, both being obtained from Prof. Maragliano. His report states that while he could not demonstrate antitoxic activity in the serum, it was bacteriolytic.

The important toxins of tubercle bacilli being of nucleoproteid nature, immunization of animals with such products results in a precipitin formation, which is so closely allied to the agglutinins as to be practically indistinguishable, since the reactions are both precipitations. Such anti-bodies are not true antitoxins, though possibly exhibiting a similar effect in the animal tissues.

Wasserman and Bruck[26] have recently demonstrated an antituberculin in the serum and tubercles of tuberculous individuals, and, in contrast to antitoxins, determined that it was of amboceptor nature. As it was present in the serum only after tuberculin was given and reactions caused, they concluded that it originated from the cells surrounding the tubercles, but was not a precipitin, which does not seem to me demonstrated by their method of testing it. According to their theory, it is formed in response to the irritation caused by tuberculin injections and combining with complement causes lysis or digestion of the stored toxin and necrosed tissue. The fever follows from the absorption of the products of lysis.

In experiments several years ago, using the same method (Bordet's[27]), I demonstrated an amboceptor in the serum of immunized cattle, but was unable to distinguish it from the agglutinin or precipitin.

The possibility of a true bacteriolytic amboceptor for tubercle bacilli is rather inferred than proved, so far as my own observation goes. Test-tube experiments and bactericidal tests are extremely unsatisfactory to demonstrate it; for even the mechanism in the animal where fresh leukocytes and complement are constantly available requires much more time than is needed for weaker bacteria.

The opsonin or the property of tuberculous serum which prepares the bacilli for phagocytosis is yet to be mentioned. Wright[27] and his associates have apparently shown that this is a specific body of complement nature. Of the importance of opsonic power to resistance we may only presume that it aids in the destruction of the bacilli. No other specific complement has been demonstrated.

As to the significance of the tuberculin reaction, for which numerous theories have been proposed, no doubt exists but that it is an expression of antagonism to the poison, and—what logically follows—also to the bacillus. The functionating cells in the reaction about the tubercle may be regarded as illustrations of local immunity, such as Wasserman has found possible against other bacteria. Such cells ordinarily serve to protect the body as a whole from the toxin by slowly absorbing it, or splitting it into soluble, simpler forms. The augmented blood flow and leukocytosis during a tuberculin reaction or extension of the disease also suggest enzyme activity. The fever and other signs of general reaction may result from the unpreparedness and injury to other cells than those in the tubercle—or as Wasserman suggested—from the products of lysis.

In this connection it may be mentioned that the phenomenon of fatal hypersusceptibility to tuberculin, which had first been ascribed by Koch to the rapid lysis of bacilli, and setting free of their poison, has recently been used to illustrate an hypothetical aggressive action on the part of the bacilli which prevents phagocytosis and toxin neutralization by the leukocytes. Our own experiments at the Saranac Laboratory have failed completely to confirm the existence of an "aggressin" secreted by virulent tubercle bacilli.

To conclude from this review of the possible antagonistic forces against tuberculosis what the processes are in a final analysis, I think we are at present justified in stating that phagocytosis with the aid of a more or less specific opsonin and agglutinin plays the leading part at first; that bacteriolysis follows immediately, also aided by specific amboceptors when sufficient time has elapsed for their development; that most important of all are the enzyme or digestive powers developed by the cells in contact with the bacilli by which the endotoxin and its products are destroyed or assimilated without damage to the organism at large; that, lastly, the tubercle, with its local reactive phenomena, gives the best insight of this mechanism at present possible.

In applying these principles to the clinical observations alluded to, one may note that phagocytic and bacteriolytic power is stimulated in some instances, and toxin-digesting and assimilating function in others, but that successful therapeutic or immunizing measures must combine both to result in ultimate good for the victim of tuberculosis. For example, the intermittent leukocytosis produced by cinnamic acid and yeast nuclein injections, the hyperemia and accompanying increased lymph flow after laparotomy in tuberculous peritonitis, the resection of joints, the suppuration and evacuation of abscesses in tuberculous lymph glands and occasionally of lung foci due to mixed infection, followed by healing, all seem explainable on the theory of an increased activity of the leukocytes and ability of the serum to exert bacteriolytic powers where otherwise the opportunity is limited by the barrier of tubercle cells.

The healing or arrest of one focus by extension of the disease elsewhere probably includes a more specific mechanism in the course of which the cells of the body everywhere being exposed to the specific products of the bacillus in the blood, become either more responsive and increasingly able to cope with the bacillus or unresponsive from overdosage or too frequent exposure. In the latter event we witness the symptoms of chronic tuberculosis, slight fever, wasting, anemia, and cachexia, with feeble tuberculin reactions. If it be thought that these statements appear too general, I must confess finally that explanations do not always explain all that may be demanded of them.

REFERENCES.

1. Welch. W. H. Huxley Lecture.

2. Smith, Theobald. Amer. Med., October 22, 1904; Jour. Exp. Med., 1898, vol. xiii, p. 451.

3. Behring, E. v. Beiträge zur exper. Therap., No. 8, 10; Congress for Tuberculosis, Paris, 1905.

4. Roemer, P. Beiträge zur exper. Therap., No. 5.

5. Roemer, P. Beiträge zur klinik der Tuberkul., 1906, vol. iv, p. 341.

6. Manfredi, L., Perez, G., Viola, P. Virchow's Archiv, vol. clv, p. 335; Ztschr. f. Hyg. u. Infek., vol. xxx, p. 64.

7. Weleminsky. Wien. klin. Woch., 1905, No. 32, p. 1010.

8. Rosenberger, R. C. Amer. Jour. Med. Sci., 1905, vol. cxxx, p. 95.

9. Bartel, J. Wien. klin. Woch., 1905, pp. 881, 1049, 1144. Bartel, J., and Neumann, W., Cent. f. Bakt. (orig.), 1906, vol. xl, pp. 518, 723.

10. Harbitz, Francis. Untersuch. über die Haufigkeit, Lokalisation und Ausbreitungswege der Tuberkulose, 1904, Jour. of Infect. Dis., 1905, vol. ii, p. 143.

11. Arneth, J. Die Lungenschwindsucht auf der Grundlage klinischen und experimentellen hematologischen Untersuchungen, 1905.

12. Ravenel, M. Jour. Med. Research, 1903, vol. x, p. 460.

13. Walsham, H. Channels of Infection in Tuberculosis, 1905.

14. Yersin. Ann. de l'Inst. Pasteur, 1888, p. 245.

15. Krompecher and Zimmerman. Cent. f. Bakt., 1903, vol. xxxiii, p. 580.

16. Weber and Bofinger. Tuberkulose Arbeiten, i, 1904.

17. Koch, R. Cent. f. Bakt., 1890, vol. viii, p. 563; Deut. med. Woch., 1890, No. 46a.

18. Trudeau, E. L. Med. Record, November 22, 1890; New York Med. Jour., July 4, 1893.

19. Arloing, S. Ref. by Weleminsky, Wien. klin. Woch., 1905, No. 32.

20. de Schweinitz, E. Medical News, December 8, 1894.

21. Pearson and Gilliland. Philadelphia Med. Jour., No. 29, 1902; PROC. PATH. SOC., Philadelphia, 1903.

22. Courmont and Dor. Etudes de la Tuberculose, 1888 to 1892; Grancher and Martin, ibid, vols. ii and iii; Hericourt and Richet, Ibid.,

23. Nichols, Joseph. Trans. Nat. Assoc. for Study and Prevention of Tuber., vol. i, 1905.

24. Blumreich and Jacoby. Ztschr. f. Hyg. u. Infek., 1898, vol. cxxix, p. 419.

25. Karwacki. Ztschr. f. Tuberkulose, 1906. vol. viii,

26. Wasserman and Bruck. Deut. med. Woch., 1906, vol. xii, p. 644.

27. Bordet, J. Ann. de l'Inst. Pasteur, 1901, vol. xv.

28. Wright, A. E. Lancet, London, 1904, p. 1138; Douglas, S. R., etc., ibid, 1905, pp. 1598, 1674.

The Prevention of Postoperative Adhesions: An Experimental Study.

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THE control of postoperative adhesions would add greatly to the resources of the modern surgeon. Considering the number of untoward conditions, not infrequently entailing secondary operations, that accrue from what appears to be undue reparatory zeal on the part of tissues injured by the manipulations of the surgeon, it is strange that more extensive studies regarding their limitation have not been made. The mechanism of the formation of adhesions has been thoroughly investigated and a number of expedients for their prevention have been suggested by various writers but none has proved sufficiently meritorious to come into general use.

In speaking of this subject McKay[1] says: "Besides attending to bands and adhesions we must not leave large denuded surfaces uncovered; if possible we may cover these, as Senn suggests, with grafts of omentum, or brush these surfaces, as August Martin does, with sterile olive oil applied with a large sponge. Morris believes that aristol is capable of forming a protective covering; but we think that Stern's suggestion that collodion should be used is absurd."

Marvel[2] regards adrenalin in warm salt solution as of value in the prevention of peritoneal adhesions. This is particularly true when old adhesions have been separated but also applies under other circumstances. The adrenalin checks oozing from the torn vessels and in this way by constricting them helps prevent the formation of exudate. In acute operative cases when actual exudate is present, absorption of that material is brought about by the salt solution, which also aids in keeping the surfaces of neighboring structures separated and the adrenalin again prevents exudate. Consequently he often places salt solution containing adrenalin in the peritoneal cavity after abdominal operations.

Wright[3] has employed for the arrest of hemorrhagic oozing a 15 to 20 per cent. solution of gelatin to which has been added 1 to 2 per cent. of formalin, the latter causing the gelatin to set in a short time. He used this in a case of hemophilia and also as a protective covering of denuded surfaces, especially of mucous membranes.

Beale[4] uses as a dressing for skin wounds a solution in acetone of a substance known under the trade name of velvril. The wound is painted with the solution and a sterile film of the dried material is then applied. The acetone is said to be unirritating to fresh wounds. He has not used the material to prevent adhesions, but this possibility is suggested by the nature of the substance. That this use might not be practicable, however, is also intimated by the fact that the film does not appear to be absorbed.

Harris[5] obtained very good results in the prevention of adhesions after operations upon the brain by the use of silver-foil. This may be placed directly upon the pia or in any other desired position. It is well tolerated by the tissues and exerts a favorable influence on healing surfaces.

Payr and Martina,[6] in reporting the results of resection of the liver by the aid of sutures passed through thin magnesium plates, state that the latter are potent in the prevention of adhesions. They ascribe this effect to the formation of a gas-containing adhesive material which entirely covers in the plates and the operation site and which does not readily unite to the surrounding tissues. The plates are said to be unirritating to the tissues and readily absorbable.

My interest in this subject was aroused by the microscopic examination of tissues obtained by Dr. Craig in his experimental studies of cargile membrane. The results of those studies have been reported in full.[7] The untimely death of Dr. Craig prevented further combined studies, but during the past summer I continued the work at leisure moments for the purpose of testing the value of several different materials. The experiments were too few in number to be deemed entirely conclusive, but they brought out certain points which possess some value in regard to further investigations of this interesting subject. All the experiments here recorded, fifteen in number, were performed upon dogs. For assistance in the operations and in working up the tissue, I am indebted to research students M. Meitzner and H. L. Hull.

Experiment I.—The right peroneal tendon was exposed for a length of 3 cm. Silver-foil was then applied, an attempt being made to wrap the tendon with strips the width of the exposed segment. This was found impossible of accomplishment in anything like a perfect manner as the foil wrinkled and tore the instant any means was employed to insert it between the tendon and the underlying tissues, adhering at once to any of them with which it came in contact. Two layers in fairly good condition were finally placed over the outer surface of the tendon and some fragments beneath it; intact layers could not be applied. The skin was sutured over the part, apparently in contact with the foil, and ten days later the wound was examined. The skin incision had healed and beneath it was a large open space enclosing the tendon and surrounded by a capsule of newly formed and forming fibrous tissue approximately 2 mm. thick. No adhesions to the tendon were found over the area occupied by the silver-foil, which was scattered irregularly through the space or attached here and there to the capsule in variously sized clumps. The enclosing newly formed tissue was firmly adherent to the under surface of the cicatrix in the skin.

Microscopically there were some polynuclear leukocytes and fibrin in the wound, one point in the superficial part appearing as though slight infection were present. This, however, was no greater than often appears in operated animals in spite of the most careful aseptic technique. The new fibrous tissue enclosed small fragments of the foil, around which were very many giant cells. Most of this tissue was placed externally, only a very small amount being on the tendon, and was continuous with the scar of the skin incision.

Experiment II.—The abdomen was opened, the peritoneum denuded from a small area of the duodenum and over it two layers of silver foil were placed. These were put on separately, the first immediately splitting nearly the entire length when applied. One layer was put on an area of intact peritoneum a short distance below the denuded site. Sixteen days later the specimen was examined. The omentum was adherent to the under surface of the wound in the belly wall and also to the denuded area of intestine covered by the foil; also to the intestine at several points near this to which fragments of the foil had been displaced. The denuded area was also firmly adherent to the lower border of the liver and to the abdominal wall overlying that point. There was no evidence of peritonitis or of intestinal obstruction. Microscopically the omentum was adherent to the intestine, and in the new tissue forming the adhesions were numerous small fragments of the foil.

Experiment III.—The peroneal tendon of the right leg was isolated for a distance of 5 cm., allowing elevation to a greater distance than was possible in Experiment I. The tendon was then wrapped with two layers of silver-foil, this being applied in a more perfect manner than before, lying fairly smooth throughout. Four days later the foil was found in bunches scattered throughout the operation site and adhesions between the tendon sheath and the surrounding tissue were present wherever the foil was lacking. Microscopically the tendon was surrounded by a layer of fibrin and leukocytes, the latter showing considerable necrosis. Within this exudate were fragments of the silver-foil. At points, especially in contact with the tendon, were numerous spindle-shaped formative cells.

These three experiments appear to indicate the impracticability of using silver-foil as a material to prevent adhesions in the situations named. It is extremely difficult to apply around tendons, and both there and in the abdomen becomes massed in small bunches which act as an irritant and apparently induce the formation of an excess of fibrous tissue. In the case of the one tendon, adhesions did not actually occur but the large space with new tissue forming around the clumps of foil was not a satisfactory termination. The indications were that the whole area would, in the course of time, have become fibrous. In the case of the brain where the foil can be applied accurately to a level surface which afterward remains practically stationary it is doubtless a valuable expedient in preventing adhesions.

Experiment IV.—The abdomen was opened and the intestinal peritoneum denuded in two areas. Over the proximal site was painted a 10 per cent. solution of gelatin, followed by a similar solution to which had been added 2 per cent. of formalin. On the distal area was painted the formalin-gelatin, mixture alone. In both instances the gelatin excited bleeding even after the flow of blood had been stopped by pressure. Probably because of this fact the gelatin did not set rapidly enough to become adherent to the surfaces and form a satisfactory protective covering. To determine if a greater quantity of formalin would aid in congelation of the gelatin and also what effect this irritating agent would produce upon the tissues an excess of formalin, at least 50 per cent., was added to the gelatin and coats of this mixture applied to both areas. Bleeding was incited, the blood and gelatin together forming a coagulum on the surfaces.

Eight days later the omentum was found to be slightly adherent to the abdominal incision and also to both the denuded areas of the intestine, slightly more firmly to the proximal site. The excess of formalin had not illy affected the intestine unless a number of small, whitish dotlets on the peritoneum proximal to each denuded area were due to its action. There was no reactive inflammation around these, however, and they were very superficial and presumably unimportant. Microscopically both areas showed essentially the same changes. The peritoneum and outer muscle layer were lacking. On the denuded surfaces was newly formed connective tissue which fastened the omentum to the intestine and sent prolongations into the inner muscle layer.

The difficulties with this method appear to be the slowness with which the gelatin sets, thus allowing bleeding to occur and apparently the actual excitation of hemorrhage by the solution, although this is in direct contrast with the findings of Wright. He used practically the double strength of the solution I employed, and this may be of some importance. Even on the peritoneum surrounding the denuded area the material did not set and adhere as it should to be effective in this work.

Experiment V.—The abdomen was opened and the peritoneum denuded from a small area of the intestine. Over this was painted a 4 per cent. solution of gutta-percha in chloroform, several coats being applied. The trial of this agent was suggested by its use by Murphy[8] as a substitute for rubber gloves in protecting the hands. This material solidified very rapidly when not interfered with by blood which again proved an annoying feature in the experiment. A film of rubber was finally obtained over a thin layer of partially clotted blood. Two coats were also painted over a like area of intact peritoneum.

Four days afterward the omentum was found to be firmly adherent to all of the denuded area. The undenuded patch which had been covered by the film was hyperemic, but adhesions were not present. No gross evidence of infection was visible. Microscopically the denuded tissue included at points the peritoneum only, occasionally the outer muscle layer also. Over the whole area were adhesions of the omentum consisting of granulation and very young fibrous tissues. Bordering this formative tissue over the denuded area was a zone of fibrinous exudate in which were numerous leukocytes. At points these were almost entirely polynuclear in type and in a few instances liquefaction of the fibrin had occurred, forming tiny foci of pus. These in no instance were extensive and healing was evident in the immediate vicinity. Over the undenuded area was a layer of fibrin containing very few leukocytes. No adhesions had formed. The gutta-percha was nowhere demonstrable.

EXPERIMENT VI.—The abdomen was opened and the peritoneum denuded from a small section of intestine. This bled profusely in spite of the use of hot water. Over this was painted several coats of a 4 per cent. solution of gutta-percha in carbon bisulphide. This rapidly solidified around the border of the wound, but there was too much blood to secure a perfect result over the denuded area. Distal to this area was placed two coats of the solution on intact peritoneum. On a third area the peritoneum was lightly scraped with a knife, then rubbed briskly with gauze, and finally covered with two coats of the solution.

Ten days later there was found adhesion of the omentum to the abdominal wound at one point where the intestine was also adherent by a short band. The denuded area of the intestine was entirely covered by adherent omentum. Distal to this and corresponding to the patch of intact peritoneum covered by solution, appeared to be a thin film of rubber, although this could not positively be determined. The third area, that which was first rubbed by gauze, could not be demonstrated. For microscopic study only the denuded area was obtained. To the entire extent the omentum was adherent by a thick layer of organizing tissue, this being particularly abundant. In it were many giant cells. A few fragments of the rubber could be detected, but all were small and inconspicuous. The new tissue extended for some distance into the inner muscle layer of the intestine, the outer layer having been removed with the peritoneum.

EXPERIMENT VII.—The left tendo-Achillis was exposed and painted with three coats of 4 per cent. gutta-percha in chloroform.

At the end of three days a small amount of inflammatory exudate was present, but appeared to be free from the tendon except at a few points on the deeper aspect, presumably where the solution had not been so thoroughly applied. Microscopically at a few points on one side of the tendon was a slight amount of exudate, chiefly of mononuclear cells.

Experiment VIII.—The abdomen was opened and an area of the intestine rubbed with gauze. A thin sheet of hardened celloidin (to be referred to later) was placed over it, but could not be made to adhere. Its use was abandoned and the surface then painted with three coats of 4 per cent. gutta-percha in chloroform. After three days the abdomen was reopened. Owing to seizure of the wrong part the wounded intestine was drawn out with considerable force before the treated area was located. The omentum did not come with it but was considerably thickened near that location and may have been adherent to the intestine. The adhesions, if any were present, must have been very slight. The rubber was rolled up in a mass at one point on the intestine. The denuded area was very hyperemic. Microscopically a slight amount of fibrinous exudate was present over the treated area. There was no evidence of adherent omentum.

Experiment IX.—The abdomen was opened and the intestine scraped with a scalpel and then rubbed with gauze until strongly hyperemic and a slight oozing had occurred. It was then painted with three coats of 4 per cent. solution of gutta-percha in chloroform. Five days later the omentum was firmly adherent to the treated area and a neighboring coil of intestine was also attached to it. Microscopically there was a thick layer of new tissue binding the omentum to the intestine, and also at one point the second coil of intestine was attached. At points in the exudate bordering the new tissue were tiny foci of suppuration.

Experiment X.—The abdomen was opened, the peritoneum removed from a small area of intestine, and the spot covered by three layers of 4 per cent. solution of gutta-percha in carbon bisulphide. Bleeding interfered with the proceeding. Forty-four days later there were found adhesions between the omentum and the scar in the abdominal wall. There was also a band-like attachment of the omentum 2 cm. in length over the denuded area of the intestine. Microscopically the rubber was not demonstrable.

Experiment XI.—The right tendo-Achillis was exposed and painted with three coats of 4 per cent. gutta-percha in xylol. At the end of three days there were uniform adhesions extending around the tendon, even on the side of the skin incision where the application could best be made. Around the deeper part of the structure was an excessive amount of inflammatory tissue. Under the microscope the exudate was found to be largely fibrin and polynuclear leukocytes. On the surface of the tendon there were at points evidence of early reparative efforts.

Experiment XII.—The left tendo-Achillis was exposed and covered with two coats of 4 per cent. gutta-percha in chloroform. At the end of five days there was found a layer of inflammatory tissue around the tendon, but on the outer surface there were no adhesions. On the deeper surface where the material could not be so well applied adhesions had formed. Microscopically there was surrounding the tendon an exudate of fibrin and leukocytes, but this was not abundant in amount. At points it showed beginning organization.

These experiments with solutions of gutta-percha in various substances indicate that either the gutta-percha or the solvent, or both, is too irritating to raw surfaces to be of value in the prevention of adhesions. They were thoroughly tested because with them a protective film is obtained more readily than by any other method employed.

Experiment XIII.—The left tendo-Achillis was exposed and wrapped with a thin sheet of hardened celloidin. This was prepared by pouring on a glass plate some moderately thick celloidin, and then quickly tilting the plate, causing the celloidin to spread out in a very thin layer. When this is dry it forms a tough, almost transparent sheet. In this particular instance the film was sterilized by immersion for two hours in 1 to 500 bichloride solution. This slightly increased the hardness of the material. At the end of three days the celloidin was found to be intact. There were a few slight adhesions between it and the surrounding tissue, but none between it and the tendon. The amount of exudate was not excessive. No infection was evident.

EXPERIMENT XIV.—The right tendo-Achillis was exposed and wrapped with a sheet of celloidin that had been treated a short time with formalin vapor and then placed for one hour in 1 to 100 bichloride solution. Ten days later the celloidin was found in place and apparently uninjured. No infection was evident. There was a thin layer of inflammatory tissue on the outer surface of the celloidin, adherent to the surrounding tissue, and also beneath on the surface of the tendon, but the celloidin was perfectly free from both these layers. Microscopically there was found on the surface of the tendon a thick layer of exudate in which organization was beginning. Externally to the celloidin were fibrin and leukocytes. There were no signs of adhesions across the intact membrane.

EXPERIMENT XV.—The right tendo-Achillis was exposed and wrapped with a sheet of celloidin that had been one-half hour in 1 to 500 bichloride solution. Forty-four days later the celloidin appeared perfectly intact. The tendon readily slipped through the cylinder formed by the film, and there appeared to be no adhesions. Microscopically there was a great deal of new fibrous tissue. The celloidin was present over most of the circumference of the tendon. At points where it overlapped or where possibly it had broken were a few tiny bands of fibrous tissue, but no actual adhesions were present. A few giant cells were in the vicinity of the celloidin fragments.

In this short series of experiments the celloidin films proved by far the most satisfactory material for use about isolated tendons. If properly prepared and rendered sterile there appears no objection to their use in such locations even if absorption does not finally occur. Before being used on human beings, however, they should be allowed to remain in animal tissues for periods much longer than were permitted in the experiments herein detailed, in order that what may be called their permanent effect be secured. Thinner films than were obtained by my crude method could doubtless be prepared. In the abdominal cavity where support by surrounding tissues to retain them in place is lacking, their use does not appear feasible. If sterilization by a method that would restore the adhesive properties of the moist celloidin, and yet retain the stability of the film, could be devised their use on free surfaces would possibly be aided.

The great desideratum of materials to be effective in preventing the formation of adhesions in the peritoneum is that they be applicable in the moist state. Solid substances of any sort yet devised must needs be anchored and sutures defeat the purpose for which application of the protective is made. The ideal material must also be a hemostatic or the oozing of blood will interfere with its application. That the material should set rapidly and remain strongly adhesive while so doing is hardly necessary to state. That there will be devised a material answering these requirements cannot now be predicted. Of its great desirability there can be no question.

May 10, 1906.

REFERENCES:

1. The Preparation and After-treatment of Section Cases, London, 1905.
2. Jour. of the Med. Society of New Jersey, December, 1905.
3. Lancet, July 9, 1904.
4. Lancet, January 17, 1903.
5. Jour. Amer. Med. Assoc., March 19, 1904.
6. Verhand. Deut. Gesellschaft f. Chirurgie, April, 1905.
7. Annals of Surgery, June, 1905.
8. Jour. Amer. Med. Assoc., March 19, 1904.

The Prognosis of Pulmonary Tuberculosis as Determined by the Morphology of the Tubercle Bacillus in the Sputum.

BY RANDLE C. ROSENBERGER, M.D.

ANYONE who has examined a large number of specimens of sputum can attest to the multiplicity of forms manifested by the tubercle bacillus.

According to Coplin, who made an exhaustive study of this organism, the bacterium varies from 1.5 micron to 6 microns in length and from 0.2 to 0.5 microns in thickness. Thick, thin, long, short, branched, beaded, and fragmented forms can be seen in the same specimen. There may be some very short and thick as well as some very long forms which may attain a size of 10 microns. Thin bacilli are generally beaded or fragmented and may be of the same length as the thick bacilli. Again, we may have short organisms so small that they are almost coccoid. By some a fragmented bacillus is considered the same as a beaded organism. According to previous studies of the writer the fragmented form of the bacillus is one which consists of two or more rod-like sections, long and short or all equally long, making up one organism. In the beaded bacillus these sections are more or less coccoid, taking at least four to make one organism, and when eight or ten are found the resemblance to a streptococcus is marked.

The real significance of the beaded, branched, and fragmented forms is the subject of controversy, but from studies made by various observers it appears that they represent degenerated forms of the organism brought about by insufficient pabulum. Besides the differences noticed in the morphology of the organism there are marked variations in tinctorial reaction, after the application of the decolorizing solution. Some bacilli remain darkly stained while others are only faintly tinged.

Craig (*Medicine*, June, 1897), in an article bearing upon the morphology of the tubercle bacillus in the sputum, seems to think that the beaded form of the organism is most often found in the sputum of rapidly advancing cases of tuberculosis. In two cases of slowly advancing disease long filamentous forms were found, and in one instance of rapidly advancing disease true branched forms were seen. He claims that it is impossible to study the branching of this organism without becoming more and more convinced that the tubercle bacillus may be of mycelial origin.

In a later article (*Medical News*, February 25, 1905), in commenting upon the morphology of the tubercle bacillus in relation to the prognosis of pulmonary tuberculosis, Craig claims that the moisture and heat of the tropics favor a rapid and more luxuriant growth of the organism.

Long filamentous forms are very common, and at least 75 per cent. of sputums containing the tubercle bacillus show them. These long forms stain well, but often present a beaded appearance; they are generally slightly curved, one end is broadened and stains more deeply, giving the organism a club shape. In 80 per cent. of sputums containing the tubercle bacillus, Craig claims that branching forms are present, which develop from what he calls a budding form. In two-thirds of such sputums there are long rods, in which at one or more points there occurs a distinct knob or bud which stains very deeply. Some bacilli have two or more branches, the parent organism being more resistant to acids and retaining the stain better than the unbranched organism. Sometimes the branched forms produce an interlacing network and are suggestive of actinomyces in appearance.

Goggia (*Annali dell Inst.*, Maragliano 1, No. 1; *Jour. Amer. Med. Assoc.*, August 20, 1904, p. 579) summarized his research upon the morphology of the tubercle bacillus, by saying that the predominance of aberrant and necrobiotic forms in the sputum is a favorable prognostic sign, as it indicates that the organism is overcoming difficulties in its own defense.

Chiesi (*Gazz. degli Ospedali e delle Cliniche*, August 14, 1904) claims that of twenty-four cases of tuberculosis the most severe forms were characterized by sputum, the bacilli in which were short and easily stained; while the sputum from milder cases showed bacilli in which marked morphological changes had occurred, and which were of poor staining qualities.

Sciallero (*Gazz. degli Ospedali e delle Cliniche*, October 23, 1904) after infecting animals with tubercle bacilli inoculated them with tuberculin, observed that the organism assumed a number of aberrant or degenerated forms. Some were thinner and others were shorter than the typical bacterium, while still others did not take the fuchsin easily or evenly. He thinks that the predominance of morphologically distorted or degenerated forms in the sputum should be regarded as a favorable sign.

The following observations are based upon the study of 146 cases of pulmonary tuberculosis taken from the tuberculous wards of the Philadelphia Hospital during the past fifteen months. The method of procedure, wherever feasible, was to examine the sputum at least once in seven to ten days. In seventy-four cases before a second examination had been made the patients died. Occasionally a patient would discharge himself by escaping over the wall, but such patients generally returned in a couple of weeks or sometimes sooner. During the fifteen months 611 specimens of sputum were personally examined. The technique employed was carbol-fuchsin for at least fifteen minutes, without heat, followed by Gabbet's solution. The prognoses given were favorable, unfavorable, and doubtful. In 109 the clinical prognosis was unfavorable, in thirty favorable, and in seven doubtful. These cases were taken at random from the wards. The examinations of the sputum were continued until death occurred or until the patient disappeared.

As mentioned previously, seventy-four cases died after one examination had been made; the number of examinations made in each case can be seen from the following table:

Cases.	Sputum examinations.	Total.
74	1	74
18	2	36
7	3	21
7	4	28
7	5	35
4	6	24
3	7	21
1	8	8
4	9	36
4	10	40
1	11	11
3	12	36
2	13	26
2	14	28
1	16	16
2	17	34
2	18	36
1	21	21
1	24	24
1	26	26
1	30	30
146		611

Of the thirty favorable cases seven are still alive, eight have died; the remainder were discharged or left of their own accord. In one case, in which there was tuberculosis of the testicle and a lesion of the right apex, no tubercle bacilli were found in the sputum after the first examination, although twelve more specimens were examined during six months.

In another instance no bacilli were demonstrable in the sputum after the fifth examination, although eight more examinations were made. The observations extended over seven months. In a third case no organisms were present in the sputum after the sixteenth examination, although eight more examinations were made, extending in all over a period of nine months. In all the other cases tubercle bacilli persisted, but their number gradually diminished and required a careful search for their detection. In the seven doubtful cases three died; the remainder, with the exception of two, passed from observation. In these last two cases examinations were carried on for nine months.

Of the 109 unfavorable cases seventy-four died before a second examination could be made. Twenty-six died in from two weeks to six months, and six are under observation at the present time. The remainder, three, left the hospital in a very precarious condition.

Of these six cases one has had thirty examinations; another twenty-six; a third twenty-four; two eighteen each, and one sixteen. These cases were under observation from six to nine months. As to the morphology of the tubercle bacillus and tinctorial characteristics, the same peculiarities were evident to the writer as have been noticed by other observers.

In the favorable cases the organisms were thin, of average size, fractured, beaded, or branched; and as arule the majority stained faintly. In several cases with an unfavorable clinical prognosis, abundant lightly staining extremely long forms of the bacillus were encountered. In the doubtful cases the organisms were almost equally distributed between the light and the dark forms.

In the unfavorable cases ninety-nine contained long, short, and average-sized bacilli staining by and retaining the carbol-fuchsin strongly. Fractured forms were common, and beaded bacilli were also encountered. In ten cases faintly staining organisms were observed, together with the dark forms. In the favorable cases in which the disease took an unfavorable turn a change in the tinctorial property of the organisms was observed. They became more darkly staining as well as more numerous. The same is true of the doubtful cases; as they advanced to a fatal termination the organisms were mostly darkly staining.

There was no characteristic variation in the physical properties between the sputums from favorable, doubtful, or unfavorable cases. Apart from the tinctorial properties of the bacilli it might be mentioned that the number of bacilli, as a rule, is greater in the unfavorable than in the favorable instances, though exceptions have been noted. This is abundantly proved by the sputum of the six unfavorable cases still remaining under observation; that is, although the bacilli are long and darkly staining they are decidedly less in number than they were in the first few examinations.

From this series of observations, it is reasonable to suppose that when an examination of the sputum shows palely staining bacilli, which are fractured, beaded, or clubbed, and of average size, the prognosis may be more favorable. On the other hand, if bacilli are observed which are short, long, or fractured, reacting intensely with the dye, the prognosis in the majority of instances should be guarded.

I wish to extend my thanks to Dr. J. T. Ullom for various courtesies and for the clinical prognoses of all the cases.

The writer wishes also to thank Drs. Wilson and Dean, resident physicians at the Philadelphia Hospital, for assistance in the accumulation of material.

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The Demonstration of Spirochæta Pallida in Lesions of Acquired Syphilis.

BY ALEXANDER A. UHLE, M.D., AND WM. H. MACKINNEY, M.D.

OF the various methods employed to establish the etiologic relation of Spirochæta pallida to syphilis, those methods dealing with its demonstration in secretions of syphilitic lesions, or in the fluids obtained from them by artificial means, have received the most attention. Schaudinn based his discovery upon positive findings in 26 cases of syphilis, the secretions being examined in a fresh state.

According to his description, the organism varies in length from 4 to 14 microns and its width does not exceed 0.5 micron. Its ends are pointed and it shows three to twelve spiral curves. It is actively motile, showing both a rotatory and longitudinal motion. Flagella have been demonstrated at either extremity.

Hoffmann, shortly after, demonstrated a spiral organism in the fluids obtained from the liver, spleen, inguinal glands, and pemphigoid eruption of a child dying of hereditary syphilis, which was in all respects similar to that described by Schaudinn.

Since this discovery, numerous observers have confirmed their finding by similar or slightly different technique. In all of these observations the findings were so constant that at the present time the causal factor of syphilis is conceded by many observers to be Spirochæta pallida, Treponema pallida, or Spironema pallida, as it is variously called.

The first attempts made to demonstrate spirochætæ in the syphilic tissue were made by Berterelli and Volpino, who succeeded in demonstrating the organism in the liver and spleen of children dying of hereditary syphilis. Their method consisted in treating very thin sections of tissue to a twenty-foar to forty-eight hours' immersion in a 0.5 per cent. solution of silver nitrate, followed by washing in a solution of pyrogallic acid and sodium acetate. They remain in this solution for fifteen minutes and are then returned to the silver solution, in which they remain until they take on a yellowish-brown color. They do not give their method in detail.

In this manner they succeeded in demonstrating Spirochæta pallida, it taking a dark-brown, almost black stain. They guarded their findings with comparisons of normal tissue.

Levaditi modified the Ramoan y Cajal method for nerve fibers, and formulated an exact method for staining syphilitic tissue *in toto*, with a view of determining the presence or absence of spirochætæ. His method has been repeatedly employed and has given satisfactory results.

It is as follows: Small pieces of tissue, not more than 2 mm. in thickness, are hardened in 10 per cent. formalin for twenty-four hours; they are then placed in 95 per cent. alcohol for the same period, and washed in water for a few hours.

Specimens are then transferred to a freshly made solution of silver nitrate (1.5 per cent.) for three successive days, changing the solution each day, and maintaining a blood temperature. Light must be excluded. This is best accomplished by placing the bottles in the incubator.

From the silver solution they are transferred to a 2 per cent. solution of pyrogallic acid, to which is added 5 per cent. of formalin.

This is also kept in the dark, but at room temperature. They are then passed through 85 per cent., 95 per cent., and absolute alcohol, embedded in paraffin and cut at about 5 microns.

By this method he succeeded in demonstrating Spirochætæ pallida in the initial lesion of syphilis and in secondary papules. Syphilitic tissue from apes inoculated with syphilis also gave positive results, as did the organs of children dying of hereditary syphilis.

A. Buschke and W. Fischer (*Berl. klin. Woch.*) employed this method successfully in demonstrating Spirochætæ pallida in a chancre and in secondary papules, without noting any particular changes in the histologic appearance of the tissue. Their most interesting discovery, however, was the finding of this organism in the heart muscle, as well as in the remaining organs of a child dying of hereditary syphilis. In this case the spirochætæ had been found in large numbers before death in the fluid obtained from an artificial cantharidal blister.

In a second article by Levaditi and Manouélian (*Compt.-rend. Soc. de biol.*, Paris, 1906) the more exact findings regarding the occurrence of Spirochætæ pallida in the primary and secondary lesions of syphilis are described. Their deductions are drawn from a study of six doubtless syphilitic lesions. They were able to demonstrate this organism in two initial lesions and in a secondary papule from the anterior belly wall. From these studies they conclude that spirochætæ reach the deeper tissues by way of the blood and lymph channels, and their appearance in large numbers in the walls and lumen of bloodvessels explains the endarteritis and periarteritis so constant in syphilis.

In six lesions removed from apes artificially inoculated with syphilis, they report positive findings in two cases, Spirochætæ pallida being found in the periphery of the ulceration, in the skin papillæ, in the wall and lumen of the bloodvessels, and in the deeper layers of the epithelium. They were unable to demonstrate organisms in the depths of the tissue.

Burent and Vincent (*Compt.-rend. Soc. de biol.*, Paris, 1906) demonstrated Spirochætæ pallida in the chancre, finding many organisms in the papillæ, and in the subepithelial connective tissue. They occurred in lymph channels and in the thickened vessel walls.

Veiklon and Girard report the findings in the roseola of syphilis. They found large numbers of Spirochætæ pallida in the capillaries of the papillæ and in the vessels beneath. From their examinations the authors conclude that the roseola is not due to a toxic activity but to embolism in the vessels of the skin papillæ, which provokes a congestive hyperemia, and perivascular infiltration similar to the roseola of typhoid. They also report positive findings in the white pneumonias of two cases of hereditary syphilis, in the adrenals of another case, and in both the maternal and fetal portions of the placenta.

Finger reports positive findings in two chancres, one being of the gangrenous type.

Ehrmann (*Dermat. Zeitsch.*, Berlin, 1906) found Spirochætæ pallida between the epithelial cells in non-ulcerated secondary lesions. The organisms were most abundant above the stratum granulosum, although present in all layers. In the papillæ they were found in greatest number, and he offers the hypothesis that those in the epithelium are extruded from the papillary bloodvessels. They are always found between the cells and never within them. He therefore concludes that not only are moist and ulcerated lesions to be considered contagious, but the dry forms as well, and should therefore be handled with great care.

E. Hoffmann and Beer (*Deutsch. med. Woch.*, 1906) call attention to a method of staining which can be carried out in less time than the Levaditi method, but the results they have obtained are no more satisfactory than those obtained by the older method. This fact is also noted by subsequent writers who employed this method, which is the following: Fixation in formalin (10 per cent.) for twenty-four hours; alcohol (95 per cent.) for fifteen hours; immersion in a 1.5 per cent. solution of silver nitrate, to which is added 10 c.c. of pure pyridin, for three hours at the room temperature, and a further three hours in the paraffin closet at a temperature of 40° to 50° C. Light must be excluded.

They are then placed in a solution made by taking 90 c.c. of a 4 per cent. solution of pyrogallic acid, to which 10 c.c. of pure acetone is added, and to 85 c.c. of this solution 15 c.c. of pure pyridine is added. The tissue remains in this solution over night, light being excluded. The tissue is then embedded and cut. Sections can be counterstained with polychrome methylene blue. By this method they succeeded in demonstrating Spirochætæ pallida in a syphilitic bubo during the secondary period of incubation and in an orbicular syphilide.

A. Blaschko (*Med. klin. Woch.*, 1906) used the Levaditi method in the study of four chancres and one condyloma. In all of these cases he reports positive findings, Spirochætæ pallida occurring in the epithelium, in the papillæ, and in the connective-tissue spaces. He found them in great numbers in the walls of bloodvessels and in their immediate vicinity. It is interesting to note that one of his specimens had remained in formalin for a year.

In July, 1906, Dr. Karl Reuter (*Zeit. f. Hygiene u. Injectionskr.*) reports several very interesting observations. He examined the tissue of a child dying of hereditary syphilis, the tissues having been preserved in formalin since 1903. The lesions included a diffuse white pneumonia, a gumma of the upper lobe of the right lung, and an interstitial pancreatitis. In all of the sections he had positive findings. In the gumma of the lung large numbers of Spirochætæ pallida were found at the periphery, underlying the limiting membrane. He could not demonstrate them in the central necrotic area. In the white pneumonic areas they occurred in less number, but were more evenly distributed. In the pancreas they were found in the interstitial connective tissue.

In a subsequent study of a recent gumma of the testicle he was unable to find spirochætæ, and cites as an analogy the difficulty of demonstrating tubercle bacilli in caseous lesions.

A series of experiments was carried out to determine the influence of mercury upon the numbers of Spirochætæ pallida found. With this object he studied three cases of hereditary and one case of acquired syphilis. In them he found it very difficult or impossible to demonstrate Spirochæta pallida after mercury had been ingested for a short time. In all of them large numbers were found prior to treatment, the examinations being made from smears of existing lesions.

The same author made studies to determine the presence of Spirochætæ pallida in cases of specific aortitis. In a patient dying suddenly of embolism, with no knowledge of syphilitic infection, and having taken no mercury, he was able to demonstrate Spirochætæ pallida in the wall of the aorta, particularly beneath the intima. This discovery is of great value in explaining the arteritis of the Döhle-Heller type.

As to the findings in tertiary lesions they are almost entirely negative. We have been unable to find positive reports in gummatous or tuberculous syphilitic lesions.

E. Tomasczewski examined the scrapings from ten tuberculous syphilides, cover-slips being made and stained by the Giemsa stain. In five of these patients he reports the presence of Spirochætæ pallida. By this method, however, the opportunity for error is so great that they can have little positive value.

Personal Observations. During the past four months we have been engaged in the study of syphilitic tissue, with the object of determining the presence or absence of Spirochætæ pallida in the lesions of acquired syphilis. In selecting the specimens care was taken to include with preference only non-ulcerated and non-eroded lesions. This was possible with the majority of papular syphilides, and to a limited extent with chancres. In tuberculous lesions the periphery was selected at a point showing the least ulceration, the object being to avoid contaminations of spiral organisms.

The method of Levaditi was employed, and we believe it to be the best method for staining the tissue *in toto*. The specimens were removed from twenty-four patients suffering with acquired syphilis, the lesions including chancres, various papular lesions, tuberculous syphilides, and one gumma.

As controls lesions of chancroids, chancroidal buboes, psoriasis, scabies, acne vulgaris, varicella, and venereal vegetations were studied.

Normal skin taken from fifteen individuals was stained in the same manner and studied.

The following is a report of the findings in each case.

Case I.—J. D. Syphilis of five months' duration. Was taking potassium iodide for two months prior to examination. There is still induration present at the site of the chancre. No syphilitic lesions were present. Has an iodide acne on the back, one being removed and examined. No spirochætæ were found.

Case II.—W. U. Chancre in sulcus. Fading, slightly pigmented macular eruption on back and chest. Macule removed from back. No spirochætæ found.

Case III.—A. H. Chancre three months ago. Profuse general eruption of large papulosquamous syphilides. No treatment. Epithelium intact. A few spirochætæ between the epithelial cells and many in the cellular infiltrate.

Case IV.—H. P. Eruption of five days' duration. History of sore on penis four weeks ago. Profuse maculopapular syphilide. Marked round-cell infiltration, but no spirochætæ found.

Case V.—H. T. Chancre in sulcus. Discrete papular syphilide. No treatment. Spirochætæ pallida found in moderate numbers in the papillæ and in the connective-tissue lymph spaces. After five weeks' treatment by mercury in pill form, no spirochætæ were found in a pigmented portion of skin removed from the back, marking the site of a syphilitic papule.

Case VI.—W. H. A. History of chancre seven months ago. Was treated at once for two months with pills, and then irregularly until five weeks ago. For the past five weeks no treatment. Now has a discrete papular syphilide on the back and mucous patches on the tongue and lip. Papule removed from back. No spirochætæ were found.

Case VII.—A. H. Syphilis of eighteen months' duration. Has been taking mercury and potassium iodide. Has an iodide acne, one lesion of which was removed. No spirochætæ were found.

Case VIII.—J. C. Chancre and general syphilitic macular eruption. Was circumcised and a part of the chancre, the skin of the prepuce, together with a mucous patch from the scrotum and a macule from the leg, were examined. Spirochætæ pallida found in moderate numbers in the chancre, mucous patch, and macule. Not found in the skin of the prepuce.

Case IX.—G. A. Syphilis of three months' duration. Has neglected treatment. Took eight mercurial inunctions and then discontinued treatment until eighteen days ago, when he began to take mercury in pill form. A fading maculopapular eruption is still present, a papule being removed. No spirochætæ were found, and very slight round-cell infiltration.

Case X.—J. Mc. Has been admitted to the Philadelphia General Hospital three times in the past eight years for the treatment of recurrent tuberculous syphilides. Has a large lesion on the left arm, a piece of which, together with the healthy adjacent skin, was removed. He has taken no treatment for the past four years. Spirochætæ present in moderate numbers. They occur in the deeper connective tissue some distance from the ulcerated surface and lying free in the lymph spaces. The adjacent skin contained no spirochætæ.

Case XI.—W. G. Chancre removed by circumcision and syphilitic papule removed from back. Spirochætæ pallida present in the chancre. In the papule the epithelium is intact. Spirochætæ pallida found in the papillæ and in the lymph spaces of the corium.

A pigmented portion of skin marking the site of a papule was removed after the patient had taken mercury in pill form for nine weeks. Examination showed no spirochætæ or cellular infiltration, the section appearing as normal skin.

Case XII.—J. W. Syphilitic papule removed from back. Had been taking mercury in pill form for three days. Spirochætæ present in small numbers between the cellular infiltrate and within the lymph spaces.

Case XIII.—P. Mc. Chancre obtained by circumcision. A maculopapular syphilide removed from back and from arm. No treatment. Chancre shows pronounced round-cell infiltration. No spirochætæ found in epithelium. The bloodvessel walls are thickened, especially the media and adventitia. A number of spirochætæ found diffusely in the tissue of the chancre and the papule of the arm, but none were found in that removed from the back.

Case XIV.—J. F. Chancre removed by circumcision and syphilitic papule removed from back. No treatment. Chancre shows marked round-cell infiltration and a moderate number of spirochætæ. The papule from the back shows but slight round-cell infiltration, and spirochætæ were demonstrated only after a most diligent examination.

Case XV.—Syphilis of several years' duration. Portion of periphery of tuberculous syphilide removed from leg. No spirochætæ were found.

Case XVI.—Syphilis of nine months' duration. Neglected treatment. Recurrent eruption, mucous patches in mouth and anal condylomas. Was circumcised and a portion of the skin of the prepuce, together with a condyloma of the anal region, examined. Spirochætæ were found in the condyloma but not in the skin of the prepuce.

Case XVII.—B. R. Treated for syphilis by mercury in pill form for eight days. Prepuce removed by circumcision; a mucous patch on it and a condyloma of the anus examined. Spirochætæ were found in the mucous patch of the prepuce, but not in the condyloma.

Case XVIII.—Chancre removed by circumcision and a syphilitic papule taken from the buttocks. No treatment. No spirochætæ were found in the chancre and the sections of the papule were also negative.

Case XIX.—J. B. Profuse maculopapular eruption present over entire body. No treatment. Spirochætæ pallida found in large numbers in a papule removed from the back. A great number were present in the skin papillæ, and some sections showed similar organisms between the epithelial cells.

Case XX.—J. K. Syphilis of fourteen months' duration. Has a large tuberculous syphilide on the right leg; a portion at the periphery of the lesion and the adjacent healthy skin were examined. In one section a few spirochætæ were found lying free in lymph spaces, and in another, after a careful search, they were demonstrated in the depth of the tissue.

Case XXI.—J. R. Chancre removed by circumcision and a papule taken from the side of the chest. Section of the chancre shows pronounced round-cell infiltration and a moderate number of spirochætæ lying between the cells. The epithelium of the papule is intact; no spirochætæ between the cells. There is a moderate infiltration of round cells and a small number of spirochætæ diffusely distributed between the cells, a few occurring around the capillaries of the papillæ.

Case XXII.—Syphilis of four years' duration. Portion of tuberculous syphilide removed from the leg. Specimen shows connective-tissue hyperplasia and moderate amount of cellular infiltrate. No spirochætæ were demonstrable.

Case XXIII.—H. P. Has two well-defined indurated ulcers on the reflected layer of the prepuce. Patient was observed for ten weeks and is still under observation, but shows no evidence of a secondary eruption on the body. At the end of ten weeks distinct mucous patches occurred on the glans penis. Prepuce was removed by circumcision and a piece of normal skin from the back. No spirochætæ were found in sections of the chancre, the skin of the prepuce or back.

CASE XXIV.—Through the kindness of Dr. A. O. J. Kelly a specimen of gumma of the brain was obtained directly from the autopsy table. A history of this patient states that he was unaware of a syphilitic infection and had never knowingly taken antisyphilitic treatment. A portion of the gumma removed from the periphery shows spirochætæ identical with those found in primary and secondary lesions of syphilis. They are present in large numbers at the periphery; the remaining tissue is necrotic.

Four lesions of psoriasis, from different patients, showed hyperplasia of the connective tissue, but nothing resembling spirochætæ. Tissue from six cases of scabies showed only a slight degree of cellular infiltration and separation of the connective tissue due to serous exudation. Three lesions of varicella from one patient showed necrotic epithelium and serous exudation. A short organism resembling a bacillus, about 4 microns in length, was found lying between the connective-tissue bundles. Nothing resembling the spirochætæ was found. Venereal vegetations from three patients showed marked papillary and connective-tissue hyperplasia, but no spirochætæ. Fifteen sections of normal skin from different individuals were examined with negative results. Nine chancroids and two chancroidal buboes were submitted to a careful examination, but with negative results.

It will be seen that observations were made upon 24 patients: subjects of acquired syphilis, from whom 34 pieces of tissue were examined. They include 7 chancres, 19 cutaneous secondary lesions, together with 3 pieces of healthy-looking skin from patients with lesions of syphilis, 4 tubercular syphilides, and 1 gumma.

In these 24 cases positive findings were obtained in 14 and negative in 10. In the patients giving a negative result 7 had received antisyphilitic treatment and 3 had not. It is the consensus of opinion that Spirochætæ pallida are not found after mercury has been taken for some time. This has been the case with the patients we have examined, the organism disappearing before the cutaneous manifestations. The time of the disappearance of the organism after the ingestion of mercury is not known. In two cases in which spirochætæ were found before the taking of mercury, none could be demonstrated after five and nine weeks of mercurial treatment. They were found in one patient after taking mercury for three days, and in one after eight days. The seven patients in whom the examinations were negative had been taking treatment from seventeen days to eighteen months.

With a few exceptions it required a careful and diligent search to determine the presence of this organism. One is very likely at times to be confused by the similar appearance of elastic tissue, and we are led to believe that observers who report the finding of large numbers of spirochætæ in the walls of bloodvessels may have made this mistake.

Spirochæta pallida is always the same no matter in what tissue it may be found, but the morphology may vary somewhat, depending upon the character and age of the lesion. Staining of tissue *in toto* is not the best means of demonstrating its morphology, and in estimating its length the cutting of the section must always be considered.

In recent lesions the organism is distinctly spiral, taking a black stain, showing from four to twelve curves, and is clear cut. In tertiary lesions it seems to lose some of its distinctness of outline and assumes a more wavy appearance. It may be found isolated or grouped in small or large numbers, and, as a rule, occurs in largest quantities in the lymph spaces. It may be demonstrated in the epithelium, but not constantly.

Spirochætæ have never been demonstrated in the healthy skin, even where this was taken directly adjoining a syphilitic lesion.

From the findings one must consider all lesions of syphilis contagious and handle them with due care.

As far as our observations go, spirochætæ are not found in other than syphilitic eruptions, occurring in subjects of syphilis.

In conclusion, we may say that the frequency with which this organism has been demonstrated in syphilitic lesions, by numerous observers, the results of inoculation experiments upon apes, and the relation which this organism bears to mercury speak in no uncertain terms for its specificity in the causation of syphilis.

We desire to thank Dr. A. O. J. Kelly for extending to us the facilities of the German Hospital Laboratory and for many courtesies extended in the preparation of this paper

We are greatly indebted to Mr. Karl Becker for valuable assistance in the preparation of the specimens. *January* 10, 1907.

A Bacteriological and Histological Study of Organs Removed from Tuberculous Subjects.

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Most of the material collected for this report was obtained from cases which came to autopsy at the Henry Phipps Institute during the writer's service there as pathologist.

The cases, with but one or two exceptions, were instances of chronic ulcerative tuberculosis, some with small and others with massive cavity formation.

The object in studying these organs was more for personal gratification than for general information, but the findings were so interesting that a presentation of the work does not seem improper. The general idea is gaining ground that when a person is affected with pulmonary tuberculosis the bacilli are spread broadcast by means of the blood or lymph, or perhaps both, when they lodge in different organs, bringing about a general systemic or visceral infection. This view seems almost positively borne out by the results of the studies about to be recorded.

The organs studied were the heart, liver, spleen, intestines, appendix, thoracic duct, and bloodvessels. The tissues were all infiltrated with paraffine; stained for histological study with hematoxylin and Van Giesen, and for tubercle bacilli with carbol fuchsin, followed with the mixture of sweet spirits of nitre and saturated alcoholic solution of malachite green.

Of 62 livers, 20 were diagnosticated macroscopically as fatty infiltration, 18 as chronic or passive congestion, 2 showed miliary tuberculosis, 1 calcified tubercles, while 2 showed amyloid infiltration. The remaining 19 organs did not show any appreciable pathological change, yet sections were stained with quite surprising results. Fifty-two livers, or 83.8 per cent., showed miliary tubercles. Some of these histological tubercles consisted only of lymphoid elements, others contained typical giant and epithelioid cells, and others showed caseation. It will be noticed that, upon gross examination, tuberculosis was diagnosticated only three times. The tubercles were situated deeply in the parenchyma, and none were found in the capsule of Glisson. As regards the intralobular or interlobular distribution, the tubercles were equally scattered. No organ showed any marked degree of increase in connective tissue, though a few showed apparently newly formed bile-ducts.

Forty-two organs studied for the presence of the tubercle bacillus gave a positive result in 41 per cent.

Citing a few authorities as regards the relative frequency of tuberculosis of the liver, Barthez and Rillet[1] found tubercles in the liver in 71 out of 312 tuberculous children. Willigk[2] in 476 autopsies of both adults and children affected with tuberculosis found the liver involved in 19. Widl[3] found nuclei and the remains of hepatic cells loaded with pigment in softened tubercles, and frequently observed the tubercles colored yellowish in the centre. Frerichs[4] mentions that tuberculous deposits in the liver at one time assume the form of gray, transparent tubercles, the size of millet seeds, and at another that of yellowish nodules, varying in size from "a lentil to a pea." They may be distributed more or less uniformly throughout the parenchyma, but are most frequently situated beneath the capsule. Softening of these tubercles terminating in the formation of small vomicæ rarely occurs, and is never so extensive as to give rise to local or general derangements, like those which result from pulmonary phthisis. Barthez and Rillet mention a case of cirrhosis associated with tuberculosis reported by Tonnelé, where its existence (tuberculosis) led to the diagnosis of cirrhotic contraction of the liver. Small vomicæ, Frerichs maintains, must not be confounded with cysts which are produced by tuberculous disease of the ducts. This condition, recognized by Rokitansky, Barrier, and Barthez and Rillet, is characterized by masses of tubercles deposited around the bile ducts, the channels of which become more and more narrowed.

As regards amyloid changes in the liver, Frerichs[4] claims that the affection rarely accompanies tubercle of the lungs and intestines.

Ullom,[5] in a study of the liver in tuberculosis, records results of an examination of 37 cases. Fatty infiltration occurred in 24 per cent., amyloid infiltration in 11 per cent., and only two organs showed an absence of passive congestion. In 30 cases, tubercles were demonstrable in 21 typical and in 9 atypical; 7 showed newly formed bile-ducts, and in 1 of the 7 there was a coincident increase of connective tissue; tubercle bacilli were observed in only 6 cases.

Pernice[6] found that the liver in tuberculosis shows certain alterations which resemble those occurring in other infections in man, and consist of a vacuolation of the protoplasm, fragmentation and destruction of chromatin, ending in a complete disintegration of the nucleus and of the cell protoplasm, so that in the place of a cell there remains only a network of residual tissue. The necrotic process is most common about the tubercles and in the neighborhood of arteries and veins, and is more extensive in cases of miliary tuberculosis, which Pernice thinks is due to special bacterial poisons.

No such changes in the liver as those described by Pernice were noticed by the writer. Besides the tuberculous changes described, fatty infiltration was observed in 32.2 per cent., passive congestion was noticed in 52 per cent., and only 12 per cent. showed amyloid infiltration.

The spleen was diagnosticated as tuberculous, macroscopically, in but 2 cases, while amyloid infiltration was recognized 9 times. In 7 instances accessory spleens (spleniculi) were encountered. These varied in size from 5 mm. to 2 cm. in diameter, were mostly globular, usually single, and attached by a short pedicle. Microscopically, 97 per cent. of the spleens showed tubercles, while in 54 per cent. tubercle bacilli were demonstrated. Even the splenculi showed histological tubercles.

In studying tuberculosis of the intestinal tract in this series of cases (62), no lesions of the esophagus, stomach, or duodenum were ever noticed. The ileum, however, was quite frequently involved, as well as the appendix. Three cases of perforation of the small intestine were observed. Thirty-six instances of tuberculosis of the intestines were met with. Of these, there were 16 in which the small and the large intestine were both involved, 9 in which the small intestine and the appendix were diseased, while 11 showed disease of the appendix alone. The lesions in the appendix were either distinct ulcers or miliary tubercles. One appendix presented the appearance of an acute catarrhal process. The remainder (10) were tuberculous, as proved by microscopic findings. In over 25 per cent. tubercle bacilli were found in the appendices examined bacteriologically.

Kelly[7] considers tuberculosis of the appendix as one of the greatest of rarities, and asserts that it may be doubted whether any well-authenticated case of primary tuberculosis of the appendix has yet been recorded. Fenwick and Dodwell (quoted by Kelly) in 2000 subjects that died of tuberculosis found that the intestine was the seat of ulceration in 500 (56.6 per cent.) out of 883 cases. It was quite exceptional to find the appendix uninvolved when there was disease of the ileocecal region. In 17 of the cases the appendix was the only portion of the intestinal tract that presented ulceration. Whether or not this ulceration was tuberculous was not definitely determined.

Haubold[8] reports a case of appendicitis in which tubercles were found in the adjacent omentum and the removed organ. No indication of pulmonary involvement was noticed at any time.

A portion of the thoracic aorta and iliac arteries was studied in a number of cases with the idea of ascertaining the effect, if any, of the tuberculous processes upon these structures. In twenty specimens no lesions of any kind were demonstrable, and the study was discontinued.

In making studies of the heart muscle, a portion of the left ventricle was always selected. In not one of the 83 cases was there the least suggestion of tubercle formation. Occasionally a small accumulation of polymorphonuclear leukocytes and lymphoid cells could be seen between the fibers, but at no time were giant cells or caseation encountered. In some sections fatty infiltration was present, and in other sections what appeared to be a fragmenting process of the myocardium was observed, as well as a beginning fibrosis. Organisms that resembled the tubercle bacillus morphologically and tinctorially were demonstrable in 8 specimens. They were quite few in number, and only by examining several sections could two or three bacilli be made out. It seems from the histological study of this organ, in this series, that the only apparent lesion is the seeming fragmentation of some of the fibers and a slight fibrosis.

In a study of the contents of the thoracic duct to determine the presence of tubercle bacilli, 22 cases were studied. The technique was as follows: The duct was dissected from the receptaculum chyli to the point of emptying into the subclavian vein. Both ends were ligated, the duct thoroughly washed in ordinary tap water, then with sterile water, and securely fastened to a block of cork and mopped thoroughly with a small piece of absorbent cotton. With a sterile hypodermic syringe the vessel was punctured and the fluid contents withdrawn. Usually but one or two drops of fluid was all that could be obtained. Spreads were then made in the ordinary way, and stained by the usual technique for tubercle bacilli. In nearly all the spreads the cellular elements were few. In some, cells resembling lymphocytes were very common, while in a few, cells resembling endothelial cells were present. Only in an occasional preparation was a polynuclear leukocyte observed. All of these 22 cases were of the chronic pulmonary variety, with the exception of 1 case of acute miliary tuberculosis.

In 16 of the cases, or 72.7 per cent., tubercle bacilli were recognized. In most of the positive cases but one or two organisms were found, and these were found only after a most patient and careful search, lasting in most instances considerably over an hour. Only in 1 case was a distinct clump of organisms seen, and this clump consisted of more than twenty bacilli. In not one of these cases was tuberculosis of the duct present, not even the slightest degree of thickening being evidenced anywhere along its entire length. In several, histological examination showed some small accumulations of lymphoid cells, but none resembling in any respect true tubercles.

Longcope,[9] in 25 cases of tuberculosis in which the process was more or less generalized, found 17 typical instances of generalized acute miliary tuberculosis. In 12 of these 17 cases the thoracic duct showed a more or less extensive tuberculous process. In 1, while there was no tuberculosis of the wall of the vessel, many tubercle bacilli were found in smears from the duct lymph. In 1 of the 4 remaining cases in which the duct was normal, there was a primary disease of one epididymis and testicle, with organized thrombi in the vesical veins containing caseous masses and tubercles. Of the 23 cases of generalized tuberculosis, 15, or over 65 per cent., showed disease of the duct, or, as in one instance, tubercle bacilli in the lymph from the duct. Of the acute cases, in over 76 per cent. the duct was affected. In 6 instances the generalized process was subacute or chronic, and while large tubercles or caseous masses were scattered in small numbers through the various organs, in only 2 was there tuberculosis of the thoracic duct. In both the tubercles were small and occurred sparingly, but in 1 a few tubercle bacilli were found in smears from the duct. In 2 other cases the tuberculous process was of a chronic character, and confined to the lungs and peritoneum. Both of these cases presented normal thoracic ducts.

Longcope's conclusions are, that tuberculosis of the thoracic duct is of great frequency in cases of acute generalized tuberculosis; and in certain cases of the acute generalized disease, tubercle bacilli may be found in the lymph from the duct, though the duct itself is not the seat of tuberculosis. In a small percentage of cases of subacute or generalized tuberculosis the duct may also be affected. Quite a number of observers—Weigert, Koch, Stilling, Benda, Brasch, and others—quoted by Longcope, have found tuberculosis present in the thoracic duct in cases of acute miliary tuberculosis.

Silbergleit,[10] in a number of cases of tuberculosis gone over for four years, claims that in 95 per cent. tubercles of the vessels or of the thoracic duct were found which had permitted the bacilli to gain the blood stream.

In conclusion, I wish to thank Dr. L. J. Spivak and undergraduate W. C. Wood for assistance in sectioning and staining the different organs.

BIBLIOGRAPHY.

1. Barthez and Rillet. Mal. des enfants, tome iii, p. 847.
2. Willigk. Prager Vierteljahrschrift, 1853, Band ii, s. 2.
3. Widl. Grundzage der Path. Hist., 1854, s. 382.
4. Frerichs. Diseases of the Liver, 1879, vol. iii, p. 4. Ibid., vol. ii, p. 177.
5. Ullom. Second Ann. Rep. Henry Phipps Inst., 1905.
6. Pernice. Riforma Medica, June 1, 1904.
7. Kelly. Deaver's Appendicitis, 3d ed., 1905, p. 138.
8. Haubold. New York Med. Jour., Feb. 3, 1906.
9. Longcope. Proc. Path. Soc. Phila., N. S., vol. viii, No. 5, 1905.
10. Silbergleit. Virchow's Archives, vol. clxxix, No. 2.

Lipoma of Uterus.

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THE uterus is an organ very frequently invaded by new-growths. Williams,[1] in a study of 13,824 patients of both sexes treated in four large London hospitals because of primary neoplasms, found that 2649, or 19.2 per cent., of the tumors were of uterine origin. Of these patients 9227 were women, and 28.7 per cent. suffered from tumor of the uterus. Of the 13,971 tumors analyzed by Gurlt, at Vienna hospitals, 4115, or 29 per cent., were uterine in location. As to the variety of tumor most frequently found in this organ, Williams' series, which may be taken as fairly representative, was made up as follows: cancer, 1571; myoma, 883; non-myomatous polyp, 191; sarcoma, 2; cystoma, 2. In this series there is no instance of the type of tumor I report, and other similar statistics attest the rarity of this growth.

According to Seydel's[2] findings, in 1903, only 4 cases of true lipoma of the uterus have been reported, and of these only 1 compares in size and location with the present specimen. Two of the 4 were tiny, cervical polyps and a third was a subserous growth the size of a cherry-stone. In addition to these 4 cases of lipoma there are on record 2 of lipomyoma and 4 of lipofibromyoma. Still another, in Lebert's *Atlas*, is designated simply as adipose tissue. Seydel accepts as authentic cases of lipomatous tumors of the uterus only these 11, rejecting 3 cases cited by Knox because they were not examined microscopically. Although at least 2 of the latter appear, from their gross description, to have been lipomas or lipofibromas, Seydel for the reason given is probably justified in excluding them from his list. The cases collated and reported by him are briefly as follows: I have verified all but 2, which I made no attempt to trace.

Lebert, in his *Atlas of Pathologic Anatomy*, 1857, pictures a uterus containing "adipose tissue." The illustration shows clearly a lobulated fibro- or musculo-fatty tumor embedded in the uterine wall.

In 1880 Stroinski reported finding a small polyp on the anterior lip of the cervix of a woman, aged twenty-eight years, who had been sterile, presumably because the growth acted as a valve to the canal. Removal of the polyp showed it to be a lipoma, and pregnancy subsequently occurred.

Orth, in 1893, makes bare mention of a cervical polyp, the size of an almond, which proved to be a lipoma.

Brünnings, in 1899, reported a case of lipomyoma, the size of a child's head, in the anterior wall of the uterus of a woman, aged fifty-five years. The tumor was interstitial in location.

Franque, in 1901, described a lipofibromyoma in a woman, aged fifty-four years. The growth was located as a cervical polyp the size of a pigeon's egg.

Knox,[3] in 1901, described in detail a lipomyoma, 10 x 13 x 10 cm. in size, located interstitially in the posterior wall of the uterus of a woman, aged sixty-two years. The symptoms and the findings at operation (hysterectomy) led to the diagnosis of uterine myoma. Further study showed the true nature of the growth.

Merkel, also in 1901, reported two cases. One was an interstitial lipoma, the size of a billiard ball, located near the right tube. The other was a lipofibromyoma the size of an orange occupying the right half of the body of the uterus of a woman, aged sixty-three years.

Jacobson, in 1902, described a lipofibromyoma found in a patient, aged sixty-eight years. The tumor was 8 cm. in diameter and was situated toward the right side in the anterior wall of the body of the uterus.

Seydel, in 1903, found a walnut-sized lipofibromyoma in the uterus of a woman, aged fifty-eight years. The specimen was an interstitial growth in the fundus.

In commenting on Seydel's case, Meyer reports in the same paper a lipoma the size of a cherry-stone found in a patient, aged forty-two years. This nodule was subserous in location, in the fundus.

The 3 cases mentioned by Knox and not accepted by Seydel are the following:

Lobstein (cited by Meckel), in 1803, described a "fatty tumor" of a uterus which enlarged the organ to the size of a seven or eight months' pregnancy.

Seegar, in 1853, reported a case occurring in a widow, aged fifty-three years. A tumor the size of a child's head protruded externally and was removed by ligation of the pedicle. Macroscopically it was a fatty tumor traversed by firm fibrous bands.

T. Smith, in 1861, showed to the Pathological Society of London a specimen from a woman, aged forty years. A pedunculated mass, the size of two fists, projected from the fundus, and proved to be largely firm fibrous tissue. Embedded in it and easily shelled out was a fatty tumor the size of a pigeon's egg.

I have found no cases in addition to those mentioned, hence the number of undoubted cases of fatty tumors of the uterus appears to be but 11, to which the 3 just mentioned should possibly be added. Several cases reported by the older writers were clearly instances of fatty degeneration of preëxisting tumors, usually myomas. Even this change is rare, McDonald[1] stating that of 530 cases of uterine fibromyoma reported by Cullingworth, Scharlieb, and Frederick only 7 showed fatty degeneration. McDonald found no instance in 280 specimens nor did Noble[5] in 278.

The specimen forming the basis of this paper was an autopsy finding in a woman, aged sixty years, who died in the Philadelphia Hospital July 19, 1906. Her family and previous medical history are recorded as negative; the ailment for which she was admitted, and which finally caused her death, was cerebral apoplexy. I am indebted to Dr. William Pickett for permission to publish the case. The pathological diagnosis included fatty heart, arteriosclerosis, chronic endocarditis, and contracted kidneys.

The uterus exhibited a globular swelling occupying the fundus and anterior portion of the body of the organ. This was much softer than is usual with uterine tumors, but was regarded as a soft myoma with possibly degenerative changes in the interior. A median incision through the organ revealed the growth to be a mass of yellow fat showing well the lamellar arrangement common to many lipomas. Spaces produced by partial separation of some of these may be seen in the gross specimen. The only suggestion of anything other than adipose tissue in the growth was at one point near the periphery where an irregular area slightly more than 1 cm. in extent appeared calcareous. Preservation of the specimen by the Kaiserling method has caused this area to become essentially as soft as the surrounding fat. The tumor measured 8 cm. in vertical and 6.5 cm. in transverse diameter. It was interstitial in location, the muscle between it and the endometrium averaging 0.5 cm. and that external 1 cm. in thickness. The growth was easily separated from the enclosing muscle and possessed what appeared to be a thin grayish capsule, though this structure could readily be detached from both the tumor and the uterine wall.

Microscopically the tumor shows the structure of a typical lipoma. The fat cells are round or polygonal in outline and for the most part much larger than those in normal adipose tissue. The nuclei are crowded to one side and flattened. The bloodvessels are not numerous and are well developed. The tumor possesses but little fibrous tissue except at points beneath what corresponds to the capsule where there are irregular bands passing for a little distance into the adipose tissue; none of them are broad and all are quite cellular. Bordering the tumor is what may be regarded as a capsule of fibrous or fibro-fatty tissue. This is more dense in the shape of a narrow band immediately surrounding the tumor proper, though even this is quite cellular and contains numerous small vessels. At points this band forms the entire boundary, but for the most part there is external to and continuous with this a network of fibrous and adipose tissues from two to three or four times the width of the described band. As a rule the adipose tissue predominates in this outer zone of the capsule, in some areas being conspicuously in excess. Over part of the extent a very narrow band of fibrous tissue forms the outer limit of this zone, but at many points almost pure adipose tissue constitutes the margin of the sections. In the tumor itself no muscle is present. At points in the capsule there is a faint resemblance to greatly attenuated muscle fibers, but, if they are such, which I doubt, they are so altered as to render identification impossible. The tumor, therefore, is a pure lipoma.

Lipomas of the uterus are of pathological and scientific rather than of clinical interest, being found accidentally at operation or at autopsy. As with most tumors, the exciting cause is unknown. The ages of the patients in the series varied from twenty-eight to sixty-eight years. That activity of the uterus has no bearing on the question may also be inferred from the fact that several of the women were sterile while one had a record of thirteen normal labors and three miscarriages.

As the normal uterus contains no adipose tissue, the histogenesis of these tumors is their most interesting feature. Their rarity is an evidence that unusual conditions obtain when they do occur. Knox considers them as supporting, in a limited way, the theory of Cohnheim regarding the histogenesis of tumors. Brünnings believes that muscle cells change into fat cells but Merkel failed to demonstrate that these cells change by substituting fat droplets for their protoplasm and believes that such metaplasia is not possible. He prefers to regard the tumors as due to hyperplasia of embryonal fat in the uterus. Franque ascribes the origin of the fat to the connective-tissue elements of the uterus, and Jacobson favors the view that similar elements in myomas become fat cells. According to his view, lipofibromyomas arise from fibromyomas by fatty infiltration of the latter.

Seydel describes degenerative changes in the cells of the stroma, but could not trace the formation of fat cells from either muscle or connective-tissue elements. He regards, as the easiest explanation, the view that these tumors spring from lipoblasts dislocated during an early period of development. Lipoblasts are not found normally around the small branches of vessels, but they may be carried there from the larger trunks, as Meyer states that he has seen fat from the parametrium extend into the substance of the uterus along with bloodvessels, but never to any great depth. Seydel is not an extreme partisan of this view. Under such circumstances both elements of a lipomyoma might develop from the walls of vessels if we accept the view that myomas arise from the muscle coat of these structures. Seydel, however, found no relation between the muscle of the tumor and the walls of the bloodvessels. As none of these or other advanced theories have been proven, it can only be said that the histogenesis of uterine lipomas is at present undetermined.

REFERENCES.

The papers of Seydel and Knox furnish a complete bibliography of the cases herein cited.

1. Williams. Bristol Med.-Chirurg. Journal, vol. xvii, No. 66, p. 314, December, 1899.

2. Seydel. Zeitsch. f. Geburts. u. Gynäk., L., pp. 274–292, 1903.

3. Knox. Johns Hopkins Hosp. Bulletin, No. 127, p. 318, October, 1901.

4. McDonald. Journal Amer. Med. Association, vol. xlii, No. 21, p. 1344, May 21, 1904.

5. Noble. Ibid., p. 1350.

September 27, 1906.

Method for the Determination of B. Typhoid and B. Coli Communis in Water and Milk.

BY H. J. SOMMERS, JR., M.D.

THE problem of isolating the bacillus of typhoid fever from water, milk, etc., has occupied the attention of many bacteriologists, and a number of methods have been presented. All, so far as I am aware, have followed the same general rule of using some acid to retard the growth of or kill all other organisms than B. typhosus or allied germs, and recommend the use of from 1 to 10 drops of the suspected liquid in about 10 c.c. of culture medium. Thus, Ufflemann, in 1891, recommended that 8 drops of a 5 per cent. solution of citric acid be added to 10 c.c. of gelatin tinged with methyl violet. He claimed that typhoid colonies present a deep-blue color and can easily be recognized. Dunbar, however, proved that B. typhosus cannot live in a medium containing citric acid in the strength recommended by Ufflemann, but that B. coli communis readily develops. Holtz, in 1890, recommended potato gelatin, acidified with 0.05 per cent. carbolic acid. Parietti in the same year recommended the use of a fluid as follows: Carbolic acid, 5 grams; hydrochloric acid, 4 grams; distilled water, 100 grams.

He recommended that three tubes, each containing 10 c.c. bouillon, be inoculated with from 1 to 10 drops of suspected water, and 3, 6, and 9 drops of the above fluid added to each of the tubes; at the end of twenty-four, forty-eight, and seventy-two hours plating is done.

Vincent, in 1890, proposed that water be introduced into a test tube containing sterile peptone bouillon, and 5 drops of a 5 per cent. solution of phenol added and the tube incubated; these methods, together with a number of others, are similar, and all result more or less frequently in failure.

In my opinion the quantity of suspected material used in such tests is often inadequate. The proof of this may be obtained from almost any bacteriologic laboratory where such examinations are made. In the laboratory of the Bureau of Health of Philadelphia I understand that upward of 2000 samples of milk were examined for B.

typhosus, all proving negative; but B. coli communis was found in many.

Being called upon to determine the source of typhoid infection in the State Hospital for the Insane at Norristown, during August, September, and October of 1905, I resorted to all of the usual methods, making several hundred inoculations, and failed to find B. typhosus, but in some instances found B. coli communis. After repeated failures, and not being able to learn of any methods other than those already used, and after giving much thought to the subject, it occurred to me that, in the first place, milk is an ideal culture medium for B. typhosus, and that Parietti's fluid in definite quantities destroys most bacteria, but leaves B. typhosus and allied organisms alive; and that, therefore, it might be advantageous to take suspected milk itself as the culture medium and to destroy most of the ordinary germ life with Parietti's fluid.

Sterile nutrient bouillon to the amount of 300 c.c. was placed in sterile flasks, infected with typhoid cultures, and various amounts of Parietti's fluid added to each flask, 2.5 c.c. up to 4 c.c. Pure cultures of B. typhosus were obtained from each. Four flasks were infected, and 4.2, 4.6, 4.6, and 5 c.c. of Parietti's fluid added, respectively; a culture was obtained from the flask containing 4.2 c.c. Parietti's fluid, the remainder being sterile. Three additional flasks were prepared and received 4.3, 4.4, and 4.5 c.c. of Parietti's fluid, respectively, and cultures were obtained from each at the end of forty-eight hours. This showed that the limit of use of Parietti's fluid was 4.5 c.c. to each 300 of liquid used. Experiments were then made with sterilized milk infected with a known B. typhosus, and after repeated trials the following method was adopted: 300 c.c. of suspected milk was introduced into each of three sterilized flasks, to which were added 3.4, 4, and 4.4 c.c. of Parietti's fluid, respectively; they were well shaken and the flasks placed in the incubator at 40° C. At the end of twenty four, forty-eight, and seventy-two hours, culture plates were made from each, and typical colonies of B. typhosus were found in one sample of suspected milk. Several other trials confirmed this, and pure cultures were carried through the various media, tested for indol and phenol, and Widal reactions were made with all suspected cultures. After demonstrating to my own satisfaction that I had found B. typhosus in the milk, water from the farm from which the infected milk was brought was obtained, and the same method was used, except that a concentrated bouillon was made and added to the water to give proper nutrient material for the growth of germ life; here also B. typhosus was found.

Subsequently it was found that the dilution of the suspected milk with about an equal quantity of boiled distilled water gave good results, and, further, that if an Erlenmeyer flask is used for this culture it should not be over one-half full, as the cream rising to the top thickens and is not readily broken when the culture is shaken to obtain material for plating unless ample room is left in the flask.

Failures in a number of cases during practical examinations where I had every reason to believe B. typhosus should be found caused me to make all first cultures anaërobic, which, of course, eliminated all aërobes with so much more chance of success; and anaërobic culture as a routine in this work is recommended.

Since the discovery of the above method, Starkey published an article[1] in which he described an original method for the isolation of B. typhosus and B. coli communis, this method depending on the motility of the germ. He used a labyrinth of glass tubing with a bulb at one end, with tubulares at the upper curvature of each limb of the labyrinth. He fills the apparatus with bouillon, acidulates with 0.05 per cent. pure carbolic acid, the openings are plugged with cotton-wool, and the whole sterilized. Inoculations are made at the bulb end, and the apparatus is then subjected to perfect anaërobic conditions and placed in the incubator. At the end of twenty-four to forty-eight hours, 1 c.c. of the fluid is removed from the individual tubulares, beginning with the one nearest the bulb, and a plate made of each. He found that the typhoid bacillus travels faster and farther than the colon bacillus, and is usually found one or two tubes ahead of the colon bacillus. In this way he was always able to obtain pure cultures of typhoid bacilli at the end of forty-eight hours.

Desiring to simplify my method and to do away with the large amounts of plating necessary, I determined to combine the two methods, and to that end had a labyrinth constructed following Starkey's plan, but in more compact form, which allows the use of a Novy anaërobic jar. The labyrinth was filled with bouillon acidulated with Parietti's fluid in the proportion of 4 c.c. to each 300 c.c. of fluid, and the whole sterilized. After cultivation for twenty-four to thirty-six hours of the suspected milk or water by the method that I have described, about 25 c.c. of the culture was added to the almost completely filled Starkey labyrinth, and as a result pure cultures of B. typhosus were readily obtained from the third or fourth tubulare at the end of twenty-four or thirty-six hours.

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[1] American Journal of the Medical Sciences, July, 1906, vol. cxxxii, p. 100.

NOTE.—The PROCEEDINGS of the Society for 1907 will be omitted and will appear in the special volume to be published in commemoration of the Fiftieth Anniversary of the founding of the Society.

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Albany Medical Annals, Albany, N. Y.
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Brazil-medico, Rio de Janeiro.
Brooklyn Medical Journal, Brooklyn, N. Y.
Buffalo Medical Journal, Buffalo, N. Y.
Bulletins et mémoires de la Société anatomique de Paris, Paris.
Cincinnati Lancet-Clinic, Cincinnati, Ohio.
Cleveland Medical Journal, Cleveland, Ohio.
Columbus Medical Journal, Columbus, Ohio.
Gazeta Lekarska, Warsaw.
Gazette des hôpitaux civils et militaires, Paris.
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Il Policlinico, Rome.
Johns Hopkins Hospital Medical Bulletin, Baltimore, Md.
Journal of Medical Research, Boston, Mass.
Journal of Mental Pathology, New York.
Lo Sperimentale, Florence.
New York Medical Journal, New York.
Nordiskt Medicinskt Arkiv, Stockholm.
Pacific Medical Journal, San Francisco, Cal.
Pennsylvania Medical Journal, Pittsburg, Pa.
Proceedings of the New York Pathological Society.
Publications of United States Department of Agriculture.
Sei-i-Kwai, Tokyo.
Studies from the Department of Pathology of the College of Physicians and Surgeons Columbia University, New York.
Surgeon-General's Catalogue.
Trabajos de Laboratorio de Investigaciones biologicas de la Universidad de Madrid.
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Transactions of the Luzerne County Medical Society, Wilkesbarre, Pa.
Transactions of the New York Academy of Medicine.
Tribuna medica, Rio de Janeiro.
Upsala Läkareförenings Förhandlingar, Upsala.
Verhandlungen der Berliner medicinischen Gesellschaft, Berlin.
Verhandlungen der Münchener medicinischen Gesellschaft, Munich.
Wisconsin Medical Journal, Milwaukee, Wis.

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THE ROLE OF PROTOZOA IN PATHOLOGY.

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It is singularly appropriate, in connection with the golden jubilee, to survey the progress which has taken place in the domain of pathology during the half century which has elapsed since the organization of this Society. And yet, so manifold and far-reaching have been the achievements of this period that one may well shrink from the task of presenting even a summary of the results obtained ; for pathology, as we know it to-day, is the product of the labors of many individuals working in many sciences. Chemistry and physics, botany and zoölogy, anatomy and embryology have each been called upon to aid in the solution of the question, as old as man himself, — the question as to the cause of disease. Fortunately, I am not expected and it is not my province to cover a subject so broad and intricate ; rather am I asked to speak upon a topic which goes to make one of the newest chapters in pathology, namely, the Protozoa.

The year in which this Society was founded marks the dawn of a new era in medicine. It was in 1857 that Pasteur, the chemist, published his first study on the mysterious phenomenon of fermentation, in which he showed, once for all, that certain microscopic globules which were smaller than those of the yeast were the cause of the conversion of sugar into lactic acid. The chemist had known for a long time that a sugar solution, plus almost any nitrogenous substance such as casein, gluten, animal matter, etc., in the presence of chalk, which served to keep the mixture neutral, would change to lactic acid. At that time the theory of Liebig as to the cause of fermentation and of most contagious diseases was dominant and, indeed, was accepted without question by all chemical workers. It rejected the idea of the influence of living matter in the production of these phenomena and held that these changes were due to the action of a ferment, an exceedingly unstable nitrogenous substance which, undergoing decomposition, excited fermentative reactions. Almost any nitrogenous matter, therefore, could act as a ferment, and for that reason it was added to the liquid to be fermented. Pasteur, however, showed that just as the yeast was necessary to change sugar into alcohol, so the "levure lactique," as he designated the microscopic globules seen by him, was needed to effect the conversion of sugar into lactic acid. He further pointed out that if almost any nitrogenous matter could bring about this change it was because such material was a suitable food for his ferment.

How little do we recognize the tremendous importance of these two fundamental observations! As a chemist Pasteur had set himself to explain and account for certain chemical phenomena. Many others had attempted the same problem, but their perspective was limited by the known methods of chemistry. He recognized the need of utilizing other methods and he found these in the microscope and in the culture flask. Equipped with these new means for investigation, Pasteur was able to enter upon that remarkable series of studies which in rapid succession revealed the nature of various fermentations and putrefactions and led to the overthrow of the doctrine of spontaneous generation. The foundations were thus laid for that era of progress in medicine, surgery and pathology, which has characterized the past half century.

In accordance with the custom of the day Pasteur looked upon the motile organisms or vibrios which he encountered as animals or infusoria. He did not concern himself with the nature of these organisms but rather with the work they did. It was enough for him to show that they were living ferments and the question as to whether they were plants or animals he left to others. Before two decades had passed, the botanist laid claim to all the bacteria and that claim has remained practically undisputed until the recent development of interest in the spirochetes.

While therefore the early studies of Pasteur pertain to bacteria and not to protozoa it is noteworthy that the experience thus obtained was soon utilized in his famous investigations (1865–1870) of one of the first known protozoal infections, namely pébrine, or the silk-worm disease. The hesitation which he experienced in taking up a study so foreign to his previous work, as he himself states, disappeared as soon as he reached the infected provinces and witnessed the ravages of the disease. He accepted the challenge of "the mysteries of nature" and at once took up the work which restored to France an industry all but destroyed. Various observers, notably the entomologist Cornalia, had noticed the presence of minute refractile globules in the diseased insects, but as to the nature of these nothing was known. Pasteur himself considered the corpuscles to be neither plants nor animals, but bodies like the cancer cells or tubercles. He accepted them, however, as diagnostic of the disease and set himself the task of discovering a means of prevention. The intuition which in his fermentation studies led him to investigate the bacteria of the air, in this case caused him to search for the Cornalian corpuscles in the dust and sweepings of the rooms where the worms were kept. He found these bodies present and by feeding healthy silk-worms with leaves spread with this infected dust he was able to reproduce the disease. Here was a notable demonstration, the first experimental transmission of a protozoal infection. The necessity of cleanliness and isolation, as a preventive measure, was then recognized and put into intelligent practice before the existence of pathogenic organisms had been demonstrated. Even before this, he recognized the fact of hereditary transmission, and on the assumption that the Cornalian corpuscle was a criterion of the disease, he based a simple method for the separation of the healthy and infected eggs. He showed that if the butterflies after oviposition were examined microscopically, and were found to be free from the corpuscles, that the eggs from such clean parents would give rise to healthy individuals. Nothing further remained than to keep this progeny under conditions excluding contact with diseased worms or their excreta.

Brief and simple as this story seems to-day it required years of painful toil to establish the facts which serve to prevent and restrict this protozoal disease. It was not until some years later that the Cornalian corpuscles were shown to be the spores of a protozoan, *Nosema bombycis*. The fact of the transmission of this parasite by means of contaminated food serves to emphasize this mode of infection in one important protozoal disease of man, namely amebic dysentery.

Amebæ. — Before the discovery of amebæ in the human intestine the known protozoan parasites of man were limited to a few flagellates and infusoria, namely *Trichomonas vaginalis* (1837), *Cercomonas hominis* (1854), *Lamblia intestinalis* (1857), and *Balantidium coli* (1857). Since then a few additional organisms of these types have been described, but they are all of little importance compared with the Ameba.

The first observation on this parasite is credited to Lambl, who in 1859, in Prague, met with small forms, supposedly amebæ, in the intestinal discharges of a patient. Later, in 1870, both Cunningham and Lewis described ameboid bodies in the stools of choleraic and other patients, but these facts attracted little attention prior to the work of Lösch (1875). It is to Lösch that we owe the term *Ameba coli* by which he designated the organism which he found in a dysenteric patient in St. Petersburg. Owing to the large numbers of the parasite and the fact that he succeeded in infecting one out of four dogs, Lösch inclined to the view that the ameba kept up the inflammatory process and that it entered after the dysenteric condition had been established. He did not ascribe a direct etiologic significance to his organism, and from the paper of Massiutkin, one of his pupils, published several years later, we may infer that he looked upon it largely as a harmless parasite.

Koch while in Egypt on the famous Cholera Commission (1883) found amebæ in several cases of dysentery and this led him to suspect that they were closely related to the disease. Kartulis was thus induced to investigate the cause of Egyptian or tropical dysentery and of liver abscess and it is to him that we owe the recognition of the causative part played by this organism (1886).

Although his observations were soon confirmed and his conclusions accepted by various workers, notably Hlava, Osler, Simon, Stengel, Musser, Dock, Councilman, and Lafleur, they were seriously questioned by others, particularly by Grassi and the Italian investigators. Opinions became divided in regard to the etiological importance of the ameba and the net result was that a number of views were set up to explain the relation of this organism to disease.

To some these parasites represented mere harmless and even useful commensals which could be found in the stools of healthy persons, or in those suffering with various diseases, as well as in those of dysentery proper. The apparent failure of some to produce in man and animals a dysenteric condition by the administration of amebæ lent color to this view. Others regarded the ameba as a potentially pathogenic agent which could manifest its action only in the intestine in which lesions had been produced by some other cause. Still others held to the view that all the amebæ as met with in the intestine are pathogenic without exception and that the apparent harmlessness arises either from a protracted latency or from antagonistic conditions which may prevail in the intestine. And finally, others consider that there are at least two species of ameba, pathogenic and non-pathogenic.

It is undesirable and certainly would be unprofitable to discuss these several views at the present time. Abundant evidence has been put forth during the past few years showing the existence of two types known respectively as bacillary and amebic dysenteries. Several kinds or varieties of bacilli have been shown to be responsible for the former and it is reasonable to believe that several species or varieties of amebæ may be concerned as etiological factors for the protozoal form of the disease.

The studies of Schaudinn certainly point to the existence of at least two species, *Entameba coli* and *Entameba histolytica*, which can be differentiated by certain morphological characteristics. This in itself must be regarded as an important advance even though his view that the former is wholly non-pathogenic does not meet with general acceptance. As Musgrave and Clegg tersely point out, the only safe hypothesis to adopt in the tropics is that all amebæ are or may become pathogenic.

The many doubts which have prevailed in the past regarding the specificity of amebæ may be said to be the necessary outcome of an incomplete method of experimentation. Although the cultivation of amebæ has been attempted, more or less successfully, by many workers during the past twenty years, it is only recently that this important subject has received the attention which it merits, and thanks to the splendid efforts of Lesage and of Musgrave and Clegg the path has been pointed out along which future investigations must proceed. The view of Schaudinn, to which Woodcock and others have given adherence, that the pathogenic protozoa are parasitic animals which are so firmly adapted in all their life manifestations to their host that no advantage can be expected from pure cultures is one which cannot be accepted in its entirety. The path of protozoal inquiry is of necessity different from that of bacteriology when it comes to the study of coccidia, malaria, and other cytozoa, but it cannot be successfully denied that in the study of those parasites which are not directly dependent upon the living host cell, as for example amebæ and trypanosomata, the pure culture is a useful and desirable if not actually a necessary condition to a thorough investigation. It is through the employment of this method that we may expect further knowledge regarding the existence of different species of amebæ, and the relation of each to the dysenteric process can then be established with that degree of exactness which the science of to-day demands. With the perfection of culture methods it will be possible to consider questions which are at present beyond reach, such as mode of action, antagonisms, etc., which have an immediate bearing on the disease itself. Hence, it cannot be too strongly urged that the morphological studies be supplemented by the cultivation tests.

Trypanosomata.—We may next direct our attention to a group of protozoa which while they have attracted general attention only during the past three or four years have nevertheless an interesting past history. It illustrates how apparently trivial scientific observations, added to from year to year, eventually lead to the accumulation of data which give a broader horizon and thus in time prepare the searcher for discoveries which have an immediate bearing on human disease. In a great measure this has been true for the large actively motile flagellates of the blood known as trypanosomes. Our knowledge of these important organisms commences with the discovery of the first member of the group in 1841 in the blood of salmon, and although during the succeeding decade a number of similar forms were described in the frog, field-mouse, mole, and rat it is more especially during the past thirty years that they have slowly come into prominence.

The observations of Lewis, in 1877, upon the flagellates of rats, captured in Calcutta, paved the way for the discovery of the first pathogenic trypanosome in the Indian surra, a disease of the horse, camel, and other domestic animals. It is an interesting coincidence that at the time when the studies of Pasteur and of Koch were directed toward the bacterial maladies, Evans in India and Laveran in Algiers, in the same year (1880) laid the foundations for the pathology of trypanosomal and malarial diseases, two of the most important protozoal infections. The overshadowing interest in the bacterial diseases and the inherent difficulties in protozoal study account for the slow progress that was made along the latter lines. Apart from the investigations of Crookshank, Danilewsky, and Lingard but little was done in the study of trypanosomes until the heuristic researches of Bruce in 1895 on the cause of the tsetse-fly disease or nagana of South Africa aroused a keen interest in protozoal inquiry, which was accentuated by the almost simultaneous work of Rouget on dourine or horse syphilis. And thus it is that during the past decade our knowledge of the trypanosomal diseases has so grown by leaps and bounds that it may be truly said these hold at present a position of commanding interest.

The reason for this is not far to seek. It is not merely because six or seven of these diseases have been recognized in domestic animals in Asia, Africa, and South America. It is not wholly due to the discovery of a human form of the disease, but rather to the fact that the mastery by man of whole regions is called into question. The successful contest with malaria and yellow fever has now given place to the fight with trypanosomiasis and upon the issue of this struggle depends to a large extent the destiny of Equatorial Africa.

Trypanosomal infections are to be met with in perhaps all parts of the world and they have been found in so many forms of animal life that it seems as if no type of vertebrate is exempt. A large number of species has been described in many amphibians, fish, birds, and mammals. Even insects, such as mosquitos, flies, and ticks, have been shown to harbor parasites of this group. In some instances, as for example in birds, we know from cultural and other characteristics that several species of birds may harbor the same trypanosome and it is equally true that a given kind of bird may be capable of infection by several kinds of flagellates. Essentially the same facts have been brought out in the study of the trypanosomal diseases of the domestic animals. Thus the surra trypanosome is found in the horse, ox, and camel and we know further that the horse is subject not only to surra but also to dourine, nagana, caderas, and dimorphon infections. In other words, under natural conditions, at least five species of trypanosomes are able to infect this one host.

The question of the plurality of the pathogenic trypanosomes, once raised by Koch but not sustained by Laveran and Mesnil and others, bids fair to be again revived by the recent studies of Ehrlich on the tolerance of a given trypanosome with reference to certain anilin dyes and arsenic preparations. It has been shown that it is thus possible to have a number of strains of the nagana trypanosome by reason of an acquired and apparently specific resistance against definite chemical bodies. If it can now be shown that animals immunized by one of these, as for example the atoxyl-fast strain, are subject to infection by the other "chemical" strains, such a fact would seriously invalidate the existing views regarding the multiplicity of species. One thing is certain, namely that the relative behavior of trypanosomes and of spirochetes to a given anilin dye cannot be accepted unreservedly as a means of differentiating species. Such results must be used with caution until considerably more has been learned about the production of varieties of a given flagellate. The differentiation of species on the basis of a life history of the organism, as desirable as that may seem, is purely theoretical since it would be difficult to find at present a single species in which the life cycle has been fully established. Hence distinctions must be based for the time being upon immunity tests and cultural characteristics whenever possible, otherwise upon the microscopical and resistant properties and upon animal reactions.

The trypanosomal infections occur not only in the warm but also in the colder countries. Thus they have been recognized in Northern Europe and only recently the presence of trypanosomes in the field mouse, rabbit, and horse have been reported from Alberta. Fortunately, the vast majority of these trypanosomes are relatively harmless parasites and may even be looked upon as non-pathogenic. The mutual immunization of host and parasite is a matter deserving of attention since it undoubtedly plays a part in the apparent freedom from illness of the host and, moreover, has a bearing on the long persistence in the blood of the parasite.

Europe and North America are singularly free from the destructive or fatal forms of trypanosomiasis. In fact the only disease of this nature, known as dourine, horse syphilis or maladie du coït, is known to occur among the breeding equines in the Mediterranean countries. Although it has been frequently reported to exist in our Western States, I am not aware that the actual identification of the infection by the finding of the trypanosome has been effected. The recent detection of the organism in a dourined horse in Alberta may therefore be said to definitely establish the presence of this disease on this Continent. On the other hand, certain parts of Asia and South America and especially Africa are subject to severe endemics of trypanosomiasis. In Africa alone seven distinct diseases of trypanosomal origin are commonly recognized and of these unquestionably the most important is the one to which man is liable.

The discovery of a trypanosome in the blood of a European in West Africa by Forde and Dutton in 1901, designated by the latter as *Trypanosoma gambiense*, opened a new chapter in human pathology. The splendid epoch-making investigations inaugurated by the Liverpool School of Tropical Medicine and rounded out by the Sleeping Sickness Commission of the Royal Society are known to all. The recognition of the trypanosomal nature of this invariably fatal affection of man was immediately followed by the discovery of its mode of propagation and upon the knowledge thus gained energetic measures for the prevention of the spread of the disease have been based. The malady is essentially a specific polyadenitis, which in the early stage is most readily diagnosed by gland palpation and by the microscopic examination of gland-juices. The later stages characterized by the invasion of the central nervous system present the condition which is known best under the name of Sleeping Sickness.

It has been shown beyond any question that the transmission of sleeping sickness is effected by the bite of the tsetse-fly, *Glossina palpalis*, and there is little doubt but that other species of this genus may also serve as transmitting agents. The ordinary biting flies (*Stomoxys*) and the mosquitos are apparently incapable of spreading the infection. As in the case of nagana, the tsetse-fly is able to convey the disease only within one or two days after it has fed on infected persons or on experimental animals. The fact that it is unable to produce an infection after two days indicates that the parasite does not multiply in the insect and does not pass through a life cycle such as has been worked out for the malarial organism.

The discovery a short time ago of flagellates in the stomach of tsetse-flies led Koch and others to believe that *Tr. gambiense* actually multiplied in the gut, but the studies of Minchin and his co-workers, and our own observations, demonstrated that these organisms were harmless parasites peculiar to the fly and in no wise related to the human trypanosome. We have been able to show that in the mosquito *Tr. Lewisi* and *Tr. Brucei* may live for at most two days and that exposure to the conditions prevailing in the stomach for a few hours is sufficient to so alter these organisms that they are no longer able to infect animals. The conclusion therefore is justified that the tsetse-fly is a mere passive and temporary carrier of the pathogenic trypanosomes and this view may be accepted for the other insect carriers of flagellates. While it is true that no cycle of development has been worked out for *Tr. gambiense* in the tsetse-fly it may be worth noting that an encysting process has been described by Minchin for *Tr. Grayi*, the common parasite of Glossina. These observations are in line with those of Prowazek on the *Herpetomonas* of the house-fly and those of Patton on the *Herpetomonas* of the mosquito. The so-called "slime cysts" occur only in the hind-gut and Minchin is of the belief that the excretion of these cysts leads to a contaminative infection of some as yet unknown vertebrate by feeding on which the tsetse-fly in turn becomes infected. It is by no means certain that the so-called cysts represent living forms, but even if this should be shown to be the case, and perhaps the best way of arriving at a solution of the question is by a study of pure cultures of the organism, it does not alter the facts regarding the transmission of *Tr. gambiense*.

A most interesting question may be touched upon at this point and that is the relation of the trypanosome of sleeping sickness to that of the South African fly disease or nagana. It is a remarkable fact that these two organisms, almost identical morphologically and about equally infective to experimental animals, should differ as they do in their behavior to man.' For it is well known that in South Africa the bite of the tsetse-fly produces no effect in man, though it causes an invariably fatal disease in the horse, dog, and some other animals. Not only is the nagana trypanosome unable to infect the human subject but by contrast it is more rapidly fatal to animals than is the trypanosome of sleeping sickness.

A partial explanation of this human immunity to *Tr. Brucei* is to be found in the fact, as shown by Laveran, that human serum has a marked injurious action on this organism. By repeated injections of such serum it is possible to prolong the lives of mice infected with *Tr. Brucei* and it is even possible to effect a cure. As a rule the injection of serum causes the organisms to disappear from the circulation, but after the lapse of some days or weeks they reappear. On repeating the injection they may be again driven out of the blood, but they soon return and after a number of such treatments the trypanosomes respond less readily to the human serum and eventually, unhindered by further injections, they multiply and cause death. It would seem therefore that under these conditions the organism acquires a tolerance for the human serum.

The extensive studies which have been recently made in the treatment of human and other trypanosomiasis by means of injections of atoxyl, para-fuchsin, trypan-red and other compounds has brought out similar facts regarding the behavior of the different trypanosomes to these remedies. While in some cases it is possible to effect a cure, in others the injections merely serve to prolong the lives of the infected animals and sooner or later the trypanosomes reappear in the blood and are no longer influenced by the treatment. These, and other extremely important facts, have been recently established by Ehrlich and it is not improbable that a clue has been found to a possible relationship of the trypanosomes of sleeping sickness and of nagana. As already indicated Ehrlich has succeeded in developing several strains of the nagana trypanosome which are resistant to and wholly uninfluenced by atoxyl, para-fuchsin, trypan-red, and trypan-blue respectively. Hence in sleeping sickness, unless the parasites are completely destroyed by the first injections of atoxyl, there is a likelihood of establishing a tolerant strain which in time will surely bring about a fatal result. The successful treatment of the human disease, it would seem, demands a rapid and almost instantaneous destruction of the parasite, and for that reason the outcome of the experimental treatment as now being carried on in Central Africa by Koch will be awaited with keenest interest.

In view of the ready production of a tolerant or non-susceptible condition in parasites the question naturally arises whether or not it is possible to grow a strain of the nagana trypanosome which will be equally resistant to human serum. The probability is that such a strain can be easily produced and if so, to what extent will that strain correspond to the trypanosome of sleeping sickness? In other words, may not *Tr. gambiense* have been originally a mere variety, so to speak, of *Tr. Brucei* which has acquired its destructive properties by repeated and brief passages through man effected by the tsetse-flies? It is hardly probable that the laboratory experiment, which of necessity is one of short duration, can effect the transformations which may have been caused by centuries of passage through the human body, but it undoubtedly will throw some light on the question of unity or plurality of trypanosomes. It is easy enough to theorize about what constitutes a species among the simplest of living forms, but it is worth bearing in mind that the protozoa as well as the protophytes are easily influenced by environmental conditions even to the extent of giving rise to a number of distinct strains or varieties. Such natural varieties have been met with in cases of sleeping sickness and also of nagana and it is probable that as our knowledge increases we will find these variations to be quite as numerous as those with which bacteriology is wrestling at present.

Kala-azar. — The interest in trypanosomiasis called forth by the discovery of the human parasite led Leishman, in 1903, to express the view that certain peculiar bodies which he found in the spleen of so-called dum-dum or cachexial fever of India were degenerated forms of trypanosomes. The same bodies were soon detected during life by Donovan, at Madras, but he was unable to find any evidence of the presence of trypanosomes. Opinions regarding the nature of the so-called Leishman-Donovan bodies became divided and while Laveran pronounced the new organism to be a *Piroplasma* (*P. Donovani*), Ross regarded it as a new form and created for it the genus *Leishmania*. Then came the remarkable discovery of Rogers that the organism when placed in citrated blood could undergo a limited multiplication resulting in the formation of typical flagellates closely related to the cultural trypanosomes. From the as yet unpublished work of Patton we know that this flagellate form also develops in the bedbug when this is allowed to feed upon patients in the last stage of the disease. Although the complete life-history of this organism is as yet unknown, there is good reason to believe that the bedbug is the carrier of the disease and it is to be hoped that the preventive measures based upon these important studies will be successful in checking the spread of this invariably fatal disease.

Curiously enough forms similar to the Leishman-Donovan bodies have been found by J. H. Wright and others in the so-called Delhi, Biskra, or Aleppo boil, but such infections appear to be purely local and non-fatal, in which respect they differ from the kala-azar of India. The systematic position of these two forms cannot be said to be established as yet, but it is quite certain that they do not belong with the *Piroplasma*, for in the human body they are not present within red blood cells but rather, as Christophers has shown, within leucocytes. The flagellate stage is very suggestive of the *Herpetomonas* and *Crithidia*, the common parasites in the gut of mosquitos, and as these can properly be considered as trypanosomes it follows that the Leishman-Donovan bodies bear some relation to this group of flagellates.

Spirochetes. — In this connection a brief consideration must be given to the interesting group of spirochetes which during the past three years have attracted no little attention. Prior to 1904, three pathogenic spirilla were known, one of these, the *Spirillum Obermeieri*, was the accepted cause of relapsing fever and the other two gave rise to fatal diseases in chicken and geese, and these by common consent were classed among the bacteria. Then came the remarkable studies of Schaudinn on the life-history of the two intracellular parasites of the owl and although his observations are open to an entirely different interpretation, as we have repeatedly shown, it must be conceded that they exerted a profound influence on pathological inquiry. The discovery of the *Spirocheta pallida*, to-day the accepted cause of syphilis, soon followed and with it came the detection of spirochetes in other conditions, so that at present these organisms rank in interest with the trypanosomes.

Schaudinn believed, and his view is still shared by some zoölogists, that the so-called leucocytozoon of the owl (*H. Ziemanni*) is essentially a blood trypanosome which, after conjugation changes in the gut of the common mosquito, gives rise to spirochete forms. Hence the view that spirochetes are trypanosomes and as such that they belong not to the bacteria but to the protozoa. The conclusion was even drawn that the spirochetes were not independent organisms but merely represented stages in the life-history of an intracellular parasite. Not one of these conclusions can be said to be established, for notwithstanding the careful studies of many workers it has not been possible to show that the other spirochetes possess a structure even remotely resembling that of trypanosomes, much less that they have an intracellular stage or that the leucocytozoon and the blood trypanosome are two stages of one and the same organism.

The recent cultivation of true spirochetes from the blood of an owl renders it more than probable that the owls, like chicken, geese, and other animals, are subject to a spirochetal disease and it follows that while Schaudinn believed he was studying two parasites he was really working with a quadruple infection. The presence of trypanosomes and spirochetes in mosquitos, captured at large, a fact not recognized at the time, still further served to complicate the question and it is certainly not in the least to the discredit of that brilliant investigator that he arrived at the explanation which his results seemingly offered.

To the physician the spirochetes are of peculiar interest because of their relation to syphilis and to relapsing fevers and possibly to other diseases. At the meeting of the Association of American Physicians last year the existence of two relapsing fevers was pointed out and a third was shown to be highly probable. *Spirillum Obermeieri*, which we owe to Norris and his co-workers, is certainly different from *Spirillum Duttoni*, as we named the cause of the African tick fever, and the work now being carried on indicates that the Eastern relapsing fever as met with in Russia, India, and the Orient is likewise different.*

The number of spirochetes has steadily grown during the past few years and it almost seems as if spirochetal infections of lower animals will be found to be as common as are those due to trypansomes. It is hardly necessary to point out the importance of giving close attention to the presence of these organisms in view of their possible bearing upon the etiology of certain diseases. Thus the recognition of a spirochete in the tumors of cancerous mice by Gaylord and Calkins, and still earlier by Borrel, raises the question of their relation to the pathological process with which they are associated. As they themselves point out, a somewhat similar spirochete (*Sp. Muris*) has been found by Wenyon and by Breinl in white and in house mice, and only recently MacNeal has recovered a similar blood parasite from the common wild rat. Is it possible for these spirochetes, primarily blood parasites, to localize in a rapidly growing tumor, or are they to be considered as the immediate cause? These are questions which obviously can only be determined by further study.

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* Recent studies have shown that the spirillum found in relapsing fever in Moscow is different from that found in New York. For geographical reasons, therefore, the name *Sp. Obermeieri* must be restricted to the Moscow organism, and the term *Sp. Novyi* has been proposed by Schellack for the New York form. Moreover, Fraenkel has shown, and we have arrived independently at the same result, that the East African Spirillum studied by Koch is essentially different from that of West Africa (*Sp. Duttoni*). For the former we would suggest the name *Sp. Kochi.* The Bombay Spirillum has recently been designated as *Sp. Carteri* by Mackie.

Although very few persons cling to the view of a trypanosomal nature of the spirochetes, the idea that they belong to the protozoa is more or less prevalent. The fact of the transmission of some of these organisms, if not all, by insects lends color to the view that they are animal organisms, but this fact, as will be presently shown, cannot be taken to represent a proof. On the other hand, many facts are known which show that in structure, multiplication, and in biological properties they are more closely allied to the bacteria than to any known form of protozoa. In the study of the protistes or lower forms of life, it is not possible to trace a sharp dividing line between the protophytes and protozoa. The most that can be hoped for is a separation into groups which bear an evident general relationship to certain recognized types. And judged from this standpoint there can be no doubt that the group of spirochetes belongs by the side of bacteria and more especially the spirilla.

Sporozoa. — Still another group of animal organism, the sporozoa, remains to be considered, and that very briefly. It includes the true cellular parasites of which the malarial organism may be taken as the type. They are apparently dependent upon the living cell as a host since not a single representative is known to exist in nature apart from the animal body. In this respect there is a marked contrast with the rhizopods and flagellates, many of which are non-parasitic by nature, while those which lead a parasitic existence live in the extracellular fluids of the body and hence are capable of artificial cultivation in the laboratory.

Of particular concern to the pathologist are those forms which live in the blood corpuscles. But while the red blood cells, for some reason not wholly understood, are favored as hosts, it is worthy of note that the leucocytes have been shown during the past few years to be subject to invasion by the so-called leucocytozoa. Such forms, however, have thus far been observed, if we except the Leishman-Donovan bodies, only in the rat, jerboa, squirrel, cat, and dog, and possibly in birds.

The parasites of the red blood cells easily rank among the most important forms with which man has to deal. The finding of the malarial organism by Laveran, in 1880, marks the beginning of a series of studies which culminated in the discovery of sexual forms by MacCallum and in the unveiling of the complete life cycle by Ross and Grassi. The recognition of the part played by the Anopheles mosquito in the transmission of the disease constitutes one of the brilliant achievements in science and we must not forget that this result was largely rendered possible by the equally remarkable demonstration of Smith and Kilborne that the Texas fever of cattle was spread through the agency of ticks. Nor must we forget that this work on ticks and mosquitos served as the basis for the still greater triumph to which American Medicine can point with just pride, the discovery of the rôle of *Stegomyia* in yellow fever.

It would be superfluous for me to enter into a discussion of the numerous studies which have contributed to our knowledge of the parasites of human malaria. But it is deserving of mention that man is not the only host for this class of parasites. Similar plasmodia are found in other animals, as monkeys, bats, squirrels, birds; and somewhat related forms, the Piroplasma, are of greatest importance as the causes of disease in various domestic animals, such as the cattle, horse, sheep, and dogs. The hemogregarines, commonly present in the cold-blooded animals, afford another example. In all parts of the world the investigation of these parasites is being pursued with a zeal which cannot but yield valuable results, and these, as in the past, may find still further application in the study of human disease.

The supposed protozoal diseases. — As is well known the etiology of many very important diseases is far from being satisfactorily established, and that notwithstanding the extraordinary efforts which have been devoted to these problems. It is only necessary to mention cancer, smallpox, scarlet fever, measles, yellow fever, rabies, and Rocky Mountain fever, to say nothing of an even larger group of animal diseases, to show some of the debatable questions of the day. In nearly all of these affections protozoa have been credited with being the causative agents, and without doubt in some, as for example in rabies, the animal parasites are factors which are seriously to be considered. The evidence, however, at present is either morphological or wholly speculative and as such is open to doubt.

While the specific inclusion corpuscles in cancer, smallpox, etc., and the equally specific Negri bodies of rabies are suggestive to some of protozoal forms, there are others who interpret these bodies as mere reactions of the animal cells, either of the nucleus, cytoplasm or both, to some unknown agent or virus, and that they may or may not envelop the real organism. The solution of these questions without doubt presents many difficulties, but it is equally certain that these are no greater than those encountered by the pioneers in bacteriological research. Whether these unknown organisms are bacteria or protozoa, visible or non-visible, cannot be at present definitely asserted. The one hope of throwing light upon these questions lies in the study of those diseases, more particularly of animals, which lend themselves to experimentation. It is only by exhaustive experimental tests and by the successful search for new methods that we may hope to gain the desired positive knowledge. Morphology alone seems powerless and hence it must be supplemented by studies bearing on the physical, chemical, and biological properties unless the crucial test — that of artificial cultivation — is first realized. The mystery of disease cannot but incite to more strenuous efforts, and the impasse in which seemingly we find ourselves to-day may be opened up in some unexpected new direction.

Modes of transmission. — One of the most interesting and at the same time most important questions which arises in the study of pathogenic organisms is that which concerns their mode of transmission. It needs no lengthy explanation to show that if we know the several ways, or let us say the common way, by which an organism gains entrance into the body, we are at once in possession of a most valuable means for the prevention of such disease. Thus, the knowledge that typhoid fever and cholera are commonly water borne enables the institution of precautionary measures of utmost practical import. Similarly, the recognition of the part played by mosquitos in malaria and yellow fever makes it possible to fight these diseases effectively by measures directed against the insect carriers, which measures have for their object either the destruction of the larval forms in their breeding places, or the direct destruction of the adult forms or their exclusion by screens from the sick and healthy persons.

Certain protozoa, notably those present in the intestine, without doubt gain admission to the body through infected food and water. In at least one trypanosomal disease, namely dourine, the evidence now at hand goes to show that infection may result from the direct application of the flagellate to the presumably uninjured mucous membrane. Just how far this mode of entrance may be utilized by other trypanosomes is not definitely known, but such facts as have been obtained go to show that this infection in other diseases is not an ordinary occurrence. The fact that dogs eating the carcasses of animals that died of surra may contract the disease is explainable on the supposition that either infection occurred through some abrasions in the mouth or throat, or that the flagellate, as in the case of dourine, is able to infect without any visible impairment of the tissues.

The transmission of most of the blood protozoa by means of insects is now a recognized fact, but the exact part played by such carriers is as yet, in many instances, not fully established. This is particularly true of the trypanosomes and spirochetes and for that reason it will not be out of place to consider the several ways by which insects may convey disease organisms.

It has been customary for some years to speak of insects as passive and as active carriers, and these terms usually convey with them certain well-defined conceptions. Thus, in a general way, the passive carrier is looked upon as conveying bacteria, whereas the active carrier is connected with the transmission of protozoa. Now to what extent, if any, can the insect be utilized in distinguishing between the two groups, bacteria and protozoa?

According to Stiles there are two general rules with reference to parasites and disease, and these it will be seen are framed along the lines indicated above. He says: "The first rule, to which at present a few exceptions are known, is that diseases which are accidentally spread by insects are caused by parasitic plants, particularly by bacteria. The second, to which no exceptions are as yet known, is that those diseases which are dependent on insects or other arthropods for their dissemination and transmission are caused by parasitic animals, particularly by sporozoa and worms."

The first rule it will be seen deals with the passive or mechanical agent of transmission, and it is certainly true that until recently the bacteria were supposed to be about the only forms thus conveyed. The studies on trypanosomes, however, have in my opinion shown that these unquestionable protozoa are transmitted in essentially the same manner. Thus the supposition that the trypanosome of sleeping sickness multiplies in the gut of the tsetse-fly has been shown to be erroneous. At all events it has been proven that the flagellates found in the stomachs of such flies are mere harmless parasites peculiar to the insect and are in nowise related to *Tr. gambiense*. The fact that the tsetse-flies must bite within a few hours after their infective feed for an infection to result goes to show that such insects are mere mechanical or passive carriers. For all practical purposes they may be compared to a syringe needle which has been dipped in infected blood. As long as the parasites remain alive on or within the needle it is possible to produce an infection by its use. The proboscis of the fly corresponds to the needle and as long as living trypanosomes are present, and that time is measured by hours, or at most by a day or two, it is capable of causing infection. These facts apparently hold good for other trypanosomal infections and hence until it is shown that these organisms actually multiply within the insect host,—and as yet, apart from Schaudinn's work, which is open to serious question, there is no evidence that this occurs, — the conclusion to be drawn is that such insects are mere passive carriers. Just as the house-fly after soiling its feet or proboscis with typhoid bacilli is in position to deposit such organisms on food and thus give rise to infection, so the biting flies in question seem to serve as mechanical agents in the transference of trypanosomes from one animal to another. It will be seen therefore that diseases which are accidentally spread by insects are not restricted to those of bacterial origin. In fact the most important diseases, from an epidemiological standpoint, thus conveyed are due to the trypanosomes. Hence the conception of a passive insect carrier to-day holds good for certain protozoa even to a greater extent than for bacteria.

Turning our attention now to insects as active carriers of disease some equally interesting deductions may be drawn. Notwithstanding the fact that it is possible experimentally to infect higher animals by injecting blood containing various plasmodia and most piroplasmes, it is true that the natural infection by such protozoa invariably occurs through the agency of insects, such as mosquitos and ticks. It is a matter of common knowledge that the malarial organism in the mosquito passes through a complex cycle of development which requires some days and must be completed before the insect is capable of transmitting the disease. A somewhat similar cycle has been recently worked out by Rogers for *Piroplasma canis*, and there can be no doubt that similar conditions obtain with hemocytozoa other than those mentioned. It will be seen therefore that under natural conditions the transmission of these diseases is dependent on insects and for that reason Stiles designates these as obligatory carriers. The artificial or accidental conveyance through wounds or by the injection of infected blood requires no special consideration, as such instances have no bearing upon the usual or natural mode of transmission.

Unlike the flies in trypanosomal diseases where the part which they play is purely passive, mechanical, and temporary, the mosquito and tick in this second type of infections are to be considered as active, diseased, and permanent carriers. It is important to recognize that these insects are diseased, and with this idea in mind we may ask ourselves whether such a condition is brought about only by protozoa.

This question it will be seen has an immediate bearing not only upon the nature of spirochetes but also upon the unknown germ of yellow fever. With reference to the spirochetes, more especially those of relapsing fever, it may be said that nearly all the facts which we have been able to gather go to show that these organisms are more closely allied to the bacteria than to any known protozoa. In one respect they approach protozoa, namely, in the fact that the tick fever spirochete (*Sp. Duttoni*) and also that of chickens, is transmitted under natural conditions through the agency of a tick. The latter plays the part of an active host since it is capable of infecting weeks and months after its feed, and further, as in the case of Texas fever, the capacity to infect may be conveyed through the egg to the young tick. In other words, the tick and its offspring become diseased. Recently some evidence has been brought forward to show that the *Spirillum Duttoni* apparently multiplies in the tick and in the egg, but this cannot be said to be fully established. In the case of the chicken spirochete the studies of Borrel and Marchoux have shown that, while this organism does not multiply in the tick (*Argas miniatus*) when the latter is kept at 15–20° C., active multiplication does occur when these insects are kept at 35° C. The spirilla then pass through the stomach wall, enter the general cavity and multiply in the organs and especially in the salivary glands and have been found in the ducts. These facts lead them to believe that a true spirillar infection of the tick results and they compare the infective power of such ticks, kept at 35° C., with that of the yellow fever mosquito, which likewise infects best when kept at an elevated temperature. Unfortunately, no data are given regarding the time which must elapse before the bite of the tick is infective, but the indication is that a definite time, as in the case of yellow fever, must elapse before the tick is infectious. From the observations of Levaditi we know that the chicken spirochete, while it will not grow in an unfertilized egg, does multiply as soon as the fertilized egg begins to develop and eventually causes the death of the chick embryo. The existence of a mild diseased condition of the tick and its young may therefore be considered as an established fact.

Elsewhere I have expressed the view that the cause of yellow fever might be found among the spirochetes and, as such, may belong not to the protozoa, as is generally accepted, but to the bacteria. The supposed protozoal nature of this unknown organism is based upon the fact that a period of about twelve days must elapse after the time the mosquito feeds upon a yellow fever patient before it is able to convey the disease, and I have been repeatedly asked how it is possible to reconcile this fact with a bacterial organism. We do know that some protozoa, like the plasmodium, require a definite time to complete their life cycle and it is equally certain that we do not know of any analogous cycle in the development of bacteria.

Although this question is purely a speculative one, it may not be out of place to advance a few considerations in the hope that they may throw some light upon the cause of this important disease. In doing this one must of necessity restrict one's self to reasoning by analogy even if the comparisons are seemingly far-fetched. It may be assumed with good reason, at the outset, that the active host, such as the malarial mosquito, is diseased and hence the persistence of the specific organism in its secretions. Now to what extent may the disease of the mosquito be compared with diseases of higher animals?

In the first place let us look at a hypothetical question that may have some bearing on the subject. Given a mild irregular fever in a higher animal, with an unknown cause, and on examination it is found that the excretory and secretory organs on about the fourteenth day of the disease allow the passage of the germ and that such elimination will now continue for months after complete recovery from the disease. In such a case a fairly definite period elapses between the first evidence of the disease and the infectiousness of the secretions. Would that fact indicate a life cycle in the development of the specific organism, and would the latter of necessity be a protozoon? Assuredly, no.

In typhoid fever we have an example of this kind. We know that the majority of typhoid patients, after about the twelfth day, eliminate the typhoid bacillus in the urine, at times in enormous numbers, and we know further that such elimination may continue for weeks and even months after apparently complete recovery has taken place. Hence such a person continues to play the part of an active host and it will be granted that he is a menace to the health of a community just as much as the diseased mosquito.

Passing by some other infections which might be cited, we can take as another example that afforded by the brilliant discoveries of the British Commission investigating Mediterranean fever. They showed that of the thousands of goats examined in Malta fully fifty per cent gave the agglutination test with *Micrococcus melitensis* and that actually ten per cent were secreting the micrococci in their milk. Such goats though apparently in good condition may continue to eliminate the micrococcus for months. Thus in one of the first tests made by Zammit, the goat after being fed on an agar culture of the organism gave milk which when examined nine months later was still crammed with micrococci. The recognition that Malta fever under natural conditions is a milk-borne disease has enabled the institution of the simplest and, at the same time, most effective measures for its suppression and is another splendid triumph in preventive medicine.

The studies on Malta fever in man present a condition analogous to that recognized in typhoid fever. That is to say, *Micrococcus melitensis* is eliminated by the kidneys for a greater or less length of time. Thus, according to Kennedy, of twenty-two cases the earliest appearance of the micrococcus in the urine was on the twenty-first day and the latest on the two hundred and forty-ninth day. In eleven of the cases the excretion continued during convalescence and there are known cases where apparently healthy persons eliminate the organism.

It will be seen from these examples that the kidney in typhoid and in Malta fevers eliminates the specific organisms and that the mammary gland in goats acts in the same way. It is worth noting that in both cases the germs are carried to the lymphatic glands and there undergo multiplication, which in the case of *M. melitensis* may be very considerable. This localization in the glands and kidneys in man and higher animals may be compared to the similar localization of the chicken spirochete and other organisms in the salivary glands of insects, and it goes without saying that a time interval between infection and elimination is needed for the latter as well as for the former. This time is necessary to allow the organism, if a bacterium, to reach the salivary glands of an insect and to multiply sufficiently until it can pass out through the secretion. In the protozoal infection of insects this time is required, in part for the life cycle, and in part for the transportation of the resulting sporozoites to the glands.

A notable demonstration of the transmission of bacteria by insects is afforded by the recent studies of the British workers in India. Although the rat flea has been supposed for some years to be the agent whereby the plague bacillus is carried to man, the evidence on this point has not been very conclusive. The British Commission, however, has definitely shown that the disease can be transmitted to the guinea-pig by the rat flea (*Pulex cheopis*). The experiments on this point are numerous and convincing and the important fact is established that such fleas may bring about an infection even after a considerable time has elapsed after they fed on the diseased persons or animal. The shortest time, however, in which infection may be produced is not known. This fact goes to show that the insect is infected and that it is not merely a temporary passive carrier.

It will be seen therefore that the function of insects as active carriers of bacteria is a possibility which must be borne in mind. Hence, the transmission of certain spirochetal diseases by ticks does not afford a serious argument against the bacterial nature of the spirochetes, and similarly, the part played by *Stegomyia* in the transmission of yellow fever does not necessarily imply a protozoal organism. In fact the evidence is strikingly suggestive of a spirochete cause. The conception of malignancy which Calkins applies to the yellow fever germ and which he associates with a supposed conjugation process is explainable quite as readily by a localization of the virus in the glands comparable to that which is now recognized in Malta fever and which is actually known to occur in the chicken tick.

An experimental solution of this question, with reference to yellow fever, is desirable and perhaps can be effected by injecting dialyzed and unaltered salt suspensions of the infected mosquito before the supposed life cycle of the protozoon has been completed. The latter should prove infectious before the twelfth day and furthermore plasmolyzed suspensions should prove equally infective.

The conclusion which can be drawn from these considerations seems to be that insects may transmit bacterial and protozoal diseases both as active and as passive carriers.

THE DYNAMIC POINT OF VIEW IN PATHOLOGY.

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When we analyze the scientific research of an historical period and contrast with it the research of another period, it becomes clear that the particular characteristics of a time are determined by two factors, the introduction of new subject matter or the discovery of new methods of investigation. Thus the chief characteristic of the physical research of this decade is associated with the discovery of the x-ray and of radium, whereby a new subject matter for research was obtained, which has led within a very short time to the erection of a scientific edifice the full magnitude of which is indicated in the recent publication of Rutherford on the Transformations of Radium. When, on the other hand, we contrast the investigations of the electric relations of chemical substances as related in the experimental researches of Faraday with those to be found in the modern books on electrochemistry, we observe vast advances that have been in large part achieved through the introduction of new methods of investigation. In a word, therefore, either a new problem may be presented or a new method of attacking old problems may be devised. History often does injustice, that is fortunately usually only temporary, because an idea may be conceived and presented to the world prematurely, at a time when the methods of investigation are not developed to the plane necessary for its demonstration. We commonly associate the names of Meyer and Hermholtz with the discovery of the law of the conservation of energy; but the simple perusal of the essay of Lavoisier and La Place upon heat will convince any one that this law was entirely familiar to them. An idea may be in advance of its time in the sense that it is in advance of the research methods of its time; in no other sense of course is a true idea ever in advance of its time. But if an idea cannot be successfully investigated or demonstrated by the methods of the time in which it was first broached, it may easily fail of appreciation and be forgotten. Later the idea may be revived, at a time when the actual investigation of the proposition is possible; and the demonstration being accomplished, the discovery of the idea is currently dated from that time. The history of science is filled with the rediscoveries of scientific ideas, many of which however have been condemned to years of oblivion, not because they were in advance of their time but because they were in advance of the editors of their time, of which sad fact the discovery by Lord Raleigh of the rejected manuscript of Waterston containing the kinetic theory of gases is a pertinent illustration. In judging of the research of a time, we must therefore in justice to the scholars of that period judge of it in the light of its methods of research. On the other hand, in judging of the status of a scientific problem, we must not accept a certain dictum simply because it is the product of the method of its time, since that scientific method may be intrinsically unadapted to the fundamental solution. We must realize that certain kinds of methods in their very nature cannot promise to yield fundamental results, and particularly those that depend to any extent upon the interpretation or personal equation of the investigator. Other methods, in their very nature, are almost completely objective and controllable, and the results achieved through their agency are susceptible of a rigid mathematical analysis and the conclusions are correspondingly secure. To this circumstance is due the fact that the science of physics is a much more stable discipline than is the science of biology.

These considerations drawn from the general sciences may I think be profitably applied to the contemplation of the subject of Pathology, to an analysis of its history, to the elucidation of its present problems, to the criticism of its methods of investigation, and to the predictions for the future.

We define pathology as the science of disease. Under this definition we include the nature of disease, the cause of disease, and the results of disease. In more specific terms we may bring the subject of pathology under three headings: etiology, of predominant importance from the point of view of preventative medicine and a subject to which too great importance cannot be attached in teaching and investigation; morbid physiology, the doctrine of the modus operandi of disease; and morbid anatomy, the doctrine of the histological lesions of tissues. The last subject has until recently greatly overshadowed the first and continues to overshadow the second, particularly in the teaching of pathology and thus secondarily in the minds of the profession of practitioners. This disproportionate predominance accorded to the visible lesions of disease is to-day out of all proper perspective and proportion and constitutes a bar to the development of the point of view of morbid physiology in clinical medicine. Pathology was born as the lineal descendant of anatomy, and physiology was regarded as only a distant connection. The anatomy of that period was a purely descriptive science. The pathology became also an almost purely descriptive science, and a review of the literature of pathology from the early days of Virchow up to the middle of the eighties illustrates that it was concerned largely with the lesions of disease, little with the causes of disease, and almost not at all with the nature of disease and the modus operandi of the morbid state. The visual lesions, partly the results of disease, in part the causes of disease, in part correlated with the disease in a manner of which the relationship is not at all clear, were the sole subject of the investigations of the pathologist. The organs were large or small, light or heavy, hard or soft, pale or congested, pigmented or unpigmented, lean or fatty, dry or watery. On microscopic examination, the minute deviations from the morphological appearances of the normal tissues were noted in a similarly exact manner.

With the advent of bacteriology, the situation changed in part. Bacteriology was during the earlier years also a descriptive science, but the parasitic relationship was so striking a situation and one so obviously inexplicable on descriptive or morphological grounds that the dynamic point of view soon forced recognition. The orthodox pathologists attempted to explain the relations of bacteria to disease in a morphological manner, of which the early formulation of the phenomenon of leucocytosis affords an excellent illustration. When the matter is looked squarely in the face, it must be realized that morphological pathology could no more elucidate or control a bacterial infection by an examination of the fixed tissues than can the deciduation of forest trees be studied by an examination of the dead leaves upon the ground. The method was fundamentally unadapted to the problem. The very perfection of the microtome has been in many respects to the detriment of progress in pathology. It is greatly to the credit of Ehrlich that he discerned early the actual plane of the situation, and devoted his efforts to the elucidation of the dynamic point of view in bacteriology.

Why, we may inquire, did not physiology influence pathology in the direction of the dynamic point of view, why did pathology become a purely morphological study, why was not the functional point of view introduced in proper perspective? Because physiology was itself largely a descriptive science. The electro-physiology was purely descriptive in the experimental sense; devoid of a chemical and physical basis, it degenerated into a recital of details. Of the whole tissue of the Du Bois Reymond electro-physiology, how much is left to-day that is adapted to the explanation of the nature and reaction of the nerve impulse? The physiological chemistry, so-called, was also largely descriptive; it was simply analytical chemistry applied to tissues. Milk contained so much protein, so much fat, so much sugar, so much ash; the ash consisted of such and such salts. The different proteins of the body differed to such and such a degree in the percentages of nitrogen, sulphur, carbon, and so forth. The work of one pure chemist, Emil Fischer, has taught us within the last few years more about the composition of protein than did all the work of the previous thirty years. The percentages of hemoglobin in the blood of the dog, cat, pig, rabbit, and in what not animals were estimated and compared; the different compositions of the skeletons of different animals were determined—and all this in the name of comparative physiology. Could anything have been more descriptive? Of course there were notable exceptions, such as Claude Bernard, but as a whole the schools of physiology were organized upon descriptive science.

For this state of affairs in physiology there were natural explanations. The majority of physiologists were offshoots from anatomy; but few entered physiology from general biology, physics or chemistry. But even had they entered by the chemical door that would for the most part have led to no striking differences, since chemistry was in that day largely descriptive and not physical or dynamic. A different state of affairs has, however, existed for nearly twenty years, and there is now no reason why the chemist who enters physiology should not have the training and the dynamic point of view of the physicist. Nevertheless, the movement to regard and teach physiology from the consistent dynamic point of view has made slow progress. When a few years ago, Loeb delivered in Columbia University a series of masterly lectures devoted to this end, the endeavor was regarded with surprise by many, with wonderment by some, and with distrust by not a few. Not only has the dynamic point of view been often absent from the physiological experiment; even under situations in which the experiment was obviously concerned with a dynamic problem, a lack of recognition of the control that should surround an experiment frequently invalidated the results. An illustration will make this clear. The conversion of glycogen into sugar in the liver, stated as a qualitative fact by Claude Bernard, has been a problem under discussion for thirty years. It is obviously a dynamic problem, not to be approached by the staining reactions of glycogen in fixed liver cells. The attempts at an elucidation of the details of this reaction have been usually concerned with analyses of blood flowing to and from the liver of a living or dead animal, associated sometimes with analyses of portions of the liver. Now such an experiment, while ostensibly a dynamic experiment, must fail, as historically it always did fail, to yield a positive result simply because the magnitudes involved were very low and the control of the variables in the experiment was impossible. To insure a positive result, the experiment must be so arranged as to deal with reliable magnitudes in measurement, and to utilize the relation of equilibrium. These conditions may be realized in lower forms of life. When, as I have recently shown, the liver of the clam is subjected to aseptic autolysis, the conversion of glycogen into sugar is shown to be a reaction of fermentation, and to follow the law of mass action.

It must not, however, be understood that the present status of physics and chemistry is such as to make it possible for the biologist to apply the physico-chemical method to all biological and medical problems. As a matter of fact, while the method is in most respects fully developed to meet the demands of the biological or medical problem, the method is not at all complete. The dynamics of pure chemistry are not fully understood, even in their grosser relations; and naturally they are not known for the more complex and complicated biological material. Of every chemical reaction we may inquire — What is the reaction? and under what conditions does the reaction proceed? There is in every reaction a driving force and an internal chemical resistance. Nearly all the work that has been devoted to the energetics of chemical reactions, that dealing with the laws of mass action, partition, and equilibrium has been concerned with the driving force. The investigations into the reactions of catalysis deal largely also with the driving force, though the internal chemical resistance is of course a direct factor, which though measured indirectly is not understood. What we need in chemistry is an Ohm's law, such as we possess in physics. This is, however, not to be achieved until the nature of internal chemical resistance is better understood. We must thus recognize that the physico-chemical method is incomplete. On the other hand, for the purpose of its applications to the larger number of present problems, in the present undeveloped state of our knowledge it stands as a reliable and serviceable method of experimentation and analysis. Organic chemistry is also of course a very incomplete science, and while it is not yet prepared for many of the problems of biology, it must be realized that its methods have never yet been exhausted in any single biological or medical problem.

An excellent illustration of the foregoing, and one that is most pertinent to the medical world, is contained in the researches of Ehrlich upon the relations between bodies and antibodies. From the beginning, the point of view of Ehrlich has been chemical and ostensibly dynamic. There are, it must be realized, two branches of the problem. The chemical and physical relations of body and antibody constitute one subject. The reaction whereby the introduction of a poison into a living body results in the formation of an antitoxine is another subject. Between these two subjects there is necessarily no connection. The first subject is obviously open to methodical chemical and physical investigation. The second is not to-day directly approachable by such methods. These distinctions were neglected by the Ehrlich school. Their experiments on the reactions between body and antibody were in part not arranged and executed in accordance with the requirements of the laws of modern chemistry; in part they were not analyzed or utilized in the mathematical sense in accordance with those laws. With the advent upon the scene of a physical chemist of the training and mental endowment of Arrhenius, these two situations were taken in hand. Those of the available experiments that were susceptible of mathematical analysis were so utilized. Beyond that, a large number of additional well-planned experiments covering all departments of the problem were carried out, and the results likewise analyzed according to the equations of known laws. As the result of these investigations it was found that within the limits of the errors of observation and experimentation the present experimental material, and it is large and well arranged, indicates that the reactions between body and antibody are to be mathematically interpreted in accordance with the laws of mass action, equilibrium, and partition. Against this type of investigation no amount of uncontrolled biological experimentation, no amount of speculation upon the properties of substances in the colloidal state will avail aught. The equations employed by Arrhenius in his calculations are, as stated by himself, in a sense provisional and interpolative, though formulated in accordance with the current usage in physical chemistry, a usage that has led to brilliant discoveries in other domains of chemical science. It is of course possible that the investigations of future years may alter the aspects of these present considerations. The physical and chemical properties of the colloidal state are little understood; when they have been elucidated it is possible that the apparent conformity of the theoretical with the observed values and magnitudes in the measurements and calculations of Arrhenius may be shown not to have warranted the direct application of the laws of mass action, equilibrium, and partition to the reactions of these substances. But the point to be emphasized here is that whatever the results of future investigations they are to be obtained only by means in conformity with accurate chemical and physical experimentation. That the point of view of Arrhenius is right and that of Ehrlich wrong has been for the present experimental material apparently shown by physico-chemical investigations; for the future to show that Arrhenius is in error the same methods alone are competent. The conclusions of Arrhenius are to be controverted only by showing upon a larger and more correctly controlled experimental material, with the same methods of mathematical analysis, that the laws of mass action, equilibrium, and partition are not applicable. Rigid experimentation and strict analysis often introduce order into a field of apparently chaotic investigation. An excellent illustration of this is to be noted in connection with the development of the study of radium. The phenomenon of so-called induced radio-activity was a few years ago in a state of lamentable confusion and the subject of much unrestful speculation. With the application by Rutherford of the rigid methods of mathematical analysis and fundamental physical experimentation, this subject has been elucidated in a manner entirely in conformity with the general point of view of mass and energy current in modern physics.

Let us now turn our attention to the dynamic point of view in pathology. The problems in pathology have in many respects undergone vast changes since the early days of Virchow. The discovery of the relations of bacteria and of protozoa to disease brought new problems into medicine. With respect to many diseases, however, the problems that to-day confront us were fully recognized thirty years ago. When one reads the studies on nephritis carried out by the German clinicians of thirty years ago, and reviews the work of Claude Bernard and Moritz Traube on diabetes, one feels that the problems in nephritis and diabetes were fully familiar to them. Methods of investigation have however improved vastly within the last thirty years, and while they have in part modified the problems by presenting to the investigator different aspects of the subjects, yet they have advanced knowledge chiefly by rendering well recognized problems open to investigation. Early pathology was descriptive, simply because the methods of the period of its renaissance were descriptive. It must be realized as a historical fact that the pathologist has practised to a noteworthy degree the faults of the biological investigator; he has described in the qualitative sense, and has connected his descriptions with speculations; he has not measured, controlled or analyzed his findings. And this all in the structural sense. In the functional sense, the pathological investigations of disease have in the main been confined to qualitative descriptions, which in comparison with the mass of morphological descriptions have been meager indeed. But it is precisely the dynamic point of view in research in pathology that practical medicine stands most in need of; and it has been largely because of the neglect of the dynamic point of view in research that pathology has contributed so little to practical medicine and to pharmacology. The sick individual representing essentially a reaction system not in equilibrium, a chemical and physical experiment, the main questions concerning the malfunctionation are: What is the qualitative reaction concerned? What abnormal reaction, if any, occurs? What are the quantitative variations? What are the relations of the reactions and velocities to the disturbed functionation?

These are the main questions for pathology and pharmacology, not in what cells is the fault located, all important though this may be for diagnosis. A survey of diseases will illustrate that for many we know in what organs or cells is the malfunctionation situated, though of the actual nature of the disease and of the modus operandi of the disturbance — essential clinically desiderata — we are almost completely ignorant. If but a small fraction of the time that has been devoted to the cutting of thin sections and the staining of them had been expended upon investigations bearing upon the actual chemical nature of disease processes, the clinician would not to-day be so poor in knowledge and so overloaded with speculation. It has unquestionably been the realization of the fact that morphological pathology does not usually strike at the real question, and the scarcely conscious feeling of despair in the present situation that has thrown the clinical world into the vortex of speculative auto-intoxication. For the infectious diseases in particular is morphological pathology of subordinate importance. The problem of etiology and prevention and the problem of the modus of bacterial intoxications and of recovery therefrom represent the two very important aspects of these groups of diseases. The histological lesions attending the bacterial infections are of subordinate interest. Yet in our curricula more attention is devoted to these lesions than to the vastly more important problems of infection. It is necessary that we realize that the methods of descriptive pathology are fundamentally unadapted to the elucidations of the modus operandi of a morbid function. Clinical medicine demands, however, above all things an understanding of this modus operandi, and thus a vast amount of descriptive morphological pathology is practically worthless to the clinician. That morbid anatomy is a branch of science for its own sake is of course understood and is not under discussion here. That researches in morphological pathology have often led to results of the greatest importance to etiology is likewise self-evident.

The contributions of morphological pathology to diagnosis have been innumerable and inestimable; compared to these, the contributions to the understanding of the modus operandi of disease have been few. The living patient represents an experiment in pathology, in the physico-chemical sense the patient is a reaction system. The clinician therefore ought to inquire: what are the reactions of the normal function concerned in the particular case? What are the chemical deviations from the normal? Are these chemical deviations of qualitative nature, in the sense that reactions not normally present are existent? Are the variations quantitative, in the sense of a reduction, or an excess of the reaction? What are the relations in time? Once a qualitative deviation is established, what are its relations to other chemical reactions in the system? It is obvious that for the elucidation of these problems from the dynamic point of view, organic chemistry must be employed for the definition of the nature of the reaction system; and for the understanding of the relations of these reactions the laws of mass action, partition, and equilibrium, and the other general laws of reaction systems, must be applied. The necessary investigation of a disease combined therefore organic and inorganic with physical chemistry. Under these circumstances, the patient must be studied from the point of view of the experimental control current in the physical sciences, since only under such conditions of investigation is it possible to relate a particular variable to a particular chemical function. These are the data the clinician requires in order to form an actual conception of the modus operandi of a morbid process. The final step in the investigation will be the attempt to reproduce the disease, and when this has been attained the process in question may be said to be understood from the chemical point of view. When the deviations in chemical reactions are elucidated, and the physico-chemical relations determined, and when finally the disease is reproducible experimentally, it will be of little importance to know whether associated with the disease the cells of a particular organ are lean or fatty, swollen or shrunken, granulated or nongranulated. So soon as a morphological alteration can be shown to be related to a chemical relation, coördinated variables in short, then the lesion acquires a positive value; so long as it is simply a descriptive fact, it has not a positive value for the actual understanding of the nature of disease. It will be noted that the chemical and physical requirements in the investigation of disease are, in their general terms and meaning, quite parallel to the requirements of Koch's laws in bacteriology. What the clinician and pathologist need to bear constantly in mind is the necessity of control in the variables of an experiment, or more strictly speaking, to have a more accurately defined and ever present consciousness of the meaning of an experiment in the sense of the pure scientist. A large part of the investigations done in pathology are in the very nature of the experiments unadapted to induction, simply because the variables have not been determined upon and controlled. With the pure scientist, the validity of the induction is directly proportional to the control of the experiment; in pathological investigations, on the contrary, the faith of the experimenter seems often to be inversely proportional to the control.

In order to illustrate in a concrete manner to what extent the static investigations in pathology fail to elicit the essential desiderata, let us briefly consider two common and important diseases — nephritis and diabetes. The point I am attempting to emphasize could be illustrated in the bacterial infections as well as in the diseases of metabolism, but I have chosen rather to utilize for this illustration nephritis and diabetes because it will be particularly advantageous to contrast these, since for nephritis the localization of the lesion has been known from the beginning, for diabetes none has until recent times been known. Under these circumstances the student of nephritis has had constantly before him the visual picture of the alterations in the renal tissues; the student of diabetes has had none such. There can be to my mind no doubt that the possession of detailed information upon the visible lesions in the kidneys has tended to depress the metabolic and dynamic investigation of nephritis; and that the absence of any known lesion in diabetes has tended to stimulate the metabolic and dynamic investigation of diabetes. The result is that we to-day know much more about the actual morbid functionation in diabetes than we do in nephritis.

The functions of the kidneys may be briefly summarized. The kidney is one of the variables in the elimination of water, salts, and organic crystalloids. Water and salt leave the body by the intestinal tract, the skin, and respiratory tract. The osmotic pressure of the blood remains quite constant, therefore it is evident that the function of the kidneys in the elimination of water and salts is a variable in part at least correlated to the functions of the other channels of elimination. The eliminations of water and salts by the alimentary, respiratory, and cutaneous tracts are more or less dependent upon external and internal accidental conditions; the function of the kidneys is then so varied as to compensate, so to speak, for these deviations, to the end that a certain physico-chemical status quo in the circulatory fluids and cells shall be maintained. As a matter of physico-chemical theory, we have here placed the cart in front of the horse; the physico-chemical relations in the fluids and cells of the body determine the renal variations, instead of the status quo being maintained by the variations in renal activity. Organic crystalloids are eliminated in the complete sense in time, though it is evident that this is to be explained naturally by the laws of equilibrium and partition, the non-permeability of the subrenal epithelium. Though these relations are not at all clear in the chemical and physical sense, it may be reasonably inferred that in the laws of mass action, equilibrium, and partition and in the physical properties of the colloid and lipoid state, the relations will find their complete and satisfactory explanation. The kidney in the normal state exhibits variations towards water, inorganic electrolytes and crystalloids, and organic electrolytes and crystalloids; it exhibits, however, no variations towards colloids and lipoids. These are completely retained. In addition to these functions the kidney possesses undoubtedly synthetic functions, of which the formation of hippuric acid may be cited as an illustration. To what an extent such synthetic and metabolic functions exist is not known.

What now are the main problems in nephritis? What is the cause of uremia? We do not know. We know that it is not caused by the retention of any known end-product of metabolism, or by any known substance. We know that it is not the result of the total retention of the normal end-products of metabolism. It is clearly not a retention intoxication at all. We are thus forced to assume one of four possibilities: either the cause of uremia is a poison generated de novo in the diseased kidneys or body; or it is due to some defect in the intermediary metabolism, connected possibly with the metabolic function of the liver or kidney; or it may be conceived to be a disturbed equilibrium in the intermediary metabolism; or lastly, uremia may be considered to be not the result of the renal lesions at all, but rather to be regarded with the renal lesions as the results of derangements of the functions of the liver, a view now being held to some degree in France. When one reviews the literature on the lesions in the kidneys in nephritis it becomes clear that all these investigations have contributed nothing to the elucidation of the problem of uremia. When one weighs carefully the problem it is equally clear that no such elucidation could have been expected from them, since the problem is essentially a dynamic one.

In nephritis we observe that the normal relation of the kidneys to the constituents of the blood plasma is disturbed; the tubules no longer retain the colloids, and we have albuminuria. That this is not a mechanical defect is shown by the fact that it is elective towards serum albumin and the globulins. There is some tendency to retain the organic crystalloids and the inorganic electrolytes, though the accurate investigations of recent years have indicated that these retentions have been greatly exaggerated, and that for long periods of time in typical instances of nephritis of all types the elimination of these substances may be entirely normal. The morphological examination of diseased kidneys has been able to define no constant relationship between lesion and albuminuria; nor is the once dogmatically stated relationship between blood pressure and albuminuria constant. It is clear, therefore, that between the variables, leakage of albumin and renal lesion, no fixed relation exists. Nor is it clear why such should have been expected, since the physico-chemical construction of the cell, which may in general terms be defined as a colloid-lipoid-crystalloid complex in a two-phase system, must be related to the permeability or non-permeability of colloid, and of this physico-chemical construction the examination of dead sections could not be expected to afford an elucidation.

In the dropsy of nephritis we observe the last of the prominent disturbances. It has not been possible to establish any constant relationship between this abnormality and any particular lesion or combination of lesions in the kidney. To the rule that dropsy is present in predominating tubular nephritis without cardiac hypertrophy and arteriosclerosis, and absent or slight in cases with marked vascular changes in the kidneys and accompanied by cardiac hypertrophy and arteriosclerosis, so many exceptions exist that the relationship has no inductive value. Now the cause of renal dropsy is entirely obscure, beyond the fact that it is not of the same type as cardiac dropsy. It is known that the osmotic pressure of the retained fluids corresponds within narrow limits to that of the normal circulating fluids. In health the body retains in its circulating fluids and in the interstices of the tissues a certain volume of a protein containing salt solution of a certain osmotic pressure; in nephritis the body retains a much larger volume of a protein containing salt solution of practically the same osmotic pressure. Obviously, if we knew the forces that determine the normal condition, we might be able to approach the solution of the dropsy in nephritis. Both the physiological and the pathological questions are purely dynamic in character.

This brief review indicates that the morphological examination of the diseased kidney has afforded no answers to the three great questions in the pathology of nephritis. The failure is due simply to the fact that the problems are essentially dynamic, and are not to be approached by any static investigation. The descriptive chemical examinations of diseased kidneys have been equally barren of results. They have determined that the organs contain so much water, so much protein, so much fat — usually no more than the normal; but these data do not bear directly upon the questions of the cause of uremia, albuminuria, and dropsy.

Prior to the recent work upon the pancreas, diabetes may be fairly said to have lacked a known lesion. The chief disturbances are the defects in the carbonous metabolism and the coma. The coma has in recent times been adequately explained as an acidosis, due to acids derived from the abnormal combustions of the fats. As a matter of fact in this we possess to-day the only auto-intoxication of known modus operandi. In just what manner an acidosis operates to derange the equilibrium of the nervous system through the abstraction of cations is not yet elucidated; this problem, however, is not peculiar to diabetes, but applies as well to experimental acid intoxication. That the diabetic has lost in part or wholly the normal faculty of sugar combustion is certain. According to our present ideas, to which the investigations of Stoklasa have contributed much, sugar in the body is burned through the stages of glyoxylic acid, lactic acid, and alcohol; and probably thereafter through acetic acid, methane and formic acid. The qualitative evidence for this theoretical scheme, which is founded upon much experimental evidence of indirect nature, rests upon the facts that these substances are present in traces in living tissues; the quantitative relations, the march of the reaction, are not yet known. Interesting in this connection is the fact that formic acid represents an early product in the condensation of carbon dioxide in plants. In diabetes, the first stage in the combustion is certainly at fault; there is evidence also that the later stages, that from lactic acid, for example, are also at fault. Whether these defects are due to an absence of the ferment, to the presence of an anti-ferment or to disturbances in the relations of equilibrium, is not known. Obviously, the problem is a purely dynamic one; and though the defect may be associated with lesions in the islands of Langerhans, microscopic descriptions of sections of these structures cannot explain the defect in the reaction of combustion. Other problems in diabetes — the cause of the toxicity of the hyperglycemia, the cause of the tendency to gangrene, and the pharmacological problem — the necessity of finding a hydrocarbon or carbohydrate that the body can burn safely and sufficiently and thus utilize as a substitute for sugar — these are all obviously dynamic problems not to be elucidated by any static or descriptive investigations into the cells of bodies dead of diabetes.

There is no need to amplify the argument further. Granted the great importance of morphological investigations for the purpose of diagnosis, for the understanding of the modus operandi of disease processes, of death from and recovery from disease, and of the scientific treatment of disease, the dynamic investigation alone offers to the clinician a fundamental basis. The treatment of disease is a dynamic proposition. This should be recognized in the courses in pathology and bacteriology. As commonly given, these are largely courses in diagnosis. The ordinary courses in bacteriology are little more than courses in descriptive botany dealing with fungi. The usual courses in pathology neglect largely to state the real problems in pathology, they fill the student instead with a mass of details of the microscopic appearance of dead cells. The student is thus denied the dynamic view-point in medicine. Entering upon the work of the profession, the practitioner finds no point of contact between the pharmacology of to-day and the pathology taught in the undergraduate course. Morbid anatomy will always be taught in great detail since it is the foundation of diagnosis. Beyond this point, however, its scope in the medical curriculum of to-day is excessive. This holds equally true for current literature. In the volumes of the first ten years of the Ergebnisse der Allgemeinen Pathologie, the most modern of our pathological periodicals, only one-eighth of the articles have been devoted to morbid physiology. The least an education in medicine can do is to endow the student with training in modern methods of work and with a fundamental point of view. This will not be accomplished until pathology is taught from the dynamic point of view of the living organism, instead of through the static investigation of dead cells.

THE NEWER PATHOLOGY.

SIMON FLEXNER, NEW YORK.

The foundation of the Pathological Society of Philadelphia was co-incident with a period of new and unparalleled development in pathology. The period immediately preceding the year 1857 witnessed the change from the study of the pathology of the organs as a whole to the study of the changes taking place in the tissues composing the organs, through which an immense impetus was given to the pursuit of pathology. Just a decade and a half before the founding of this Society, Rokitansky's Handbook of Special Pathological Anatomy appeared in which for the first time were set up exact types of disease in place of the earlier symptomatic classification. Even while the first meetings of this Society were being held, an event was transpiring which was destined to revolutionize the medical conceptions of the time, and to place pathology on that firm foundation which has not yet been shaken, and incidentally to exert a fructifying influence upon the growth of scientific medicine which had before been unexampled. I refer to the publication in 1858 of Virchow's Lectures on Cellular Pathology. While this propitious event does not mark the new era in pathology inaugurated by the brilliant author of the lectures, it forms the basis of the belief in the cell as the ultimate seat of diseases, which deeper studies into the complex and intricate nature of cell architecture and function have only served to strengthen.

The first quarter century of the Society's history covers a period of rapid expansion of knowledge through the dominion of cellular pathology and pathological physiology. But auspicious as were the beginnings of this Society, and the first twenty-five years of its activities, the second quarter century of its history was destined to be no less auspicious. The announcement of the discovery of the tubercle bacillus in 1882 inaugurated a second new era of discovery. This momentous event preceded as it was by epoch-making studies on fermentation by Pasteur, out of which a new and beneficent surgery had already sprung, was destined for a second time in the short period of twenty-five years deeply to impress the direction and force of pathological investigation. The first quarter century of the Society's history corresponds with the era of anatomical and physiological pathology, and the second quarter century coincides with what may be called the era of etiological pathology. For while the study of the anatomical changes induced in cells by disease has not been exhausted, and each year adds valuable stores to our knowledge of the pathological changes underlying disease-processes, yet the most significant advances are being made by the study of the nature and mode of action of the causes of disease. The hope for the immediate future lies in the further study, by every means that physical and biological science can supply, of the infective diseases. Without wishing to disregard for a moment the high claims to study and the great importance of that class of diseases — chronic and constitutional so-called — which probably are not caused by microbic agents in the direct sense, I yet think that it is by following the clues already supplied, and by utilizing the finer methods already discovered for the deeper studies of the infectious diseases that the best hope lies at present. I should not wish to restrict investigation to this one class to the entire neglect of the other class of disease; for I appreciate that it is only through effort to solve the riddle of disease that discovery will ensue. The energies of investigation should be divided and part of the best strength should be exercised on the problems of the causation of the chronic and constitutional diseases. But it cannot be hoped that rapid and sure success will be achieved soon; and the traveler into those undiscovered but much explored fields of medicine should be well equipped for the journey which should not be undertaken in the spirit of a holiday jaunt, or even of a foraging expedition, for he will find few shaded sylvan haunts in which to repose calmly, or riches which are to be easily acquired by a piratical attack.

Rather he must carry with him much enthusiasm for difficult work and for following devious paths ending blindly, through which he must retrace his weary steps, and he must possess strength to bear with courage and even with a sense of pleasure those disappointments from which the less gifted and determined traveler turns back dispirited.

Fortunately, the whole civilized world has been electrified, as it were, into activity by the brilliant discoveries of the past two decades, and State provisions and private philanthropy have begun to take the direction of supporting investigations into the causes of disease. What is particularly hopeful is that no restriction has been placed upon the scope of the work, which fortunately has been made to include the whole animate world. For while it is understood that it is the human race that is to be the beneficiary of this study, the fact has come to be recognized that man does not occupy an independent position in the created system, but is acted on and reacts upon other living beings. The great complexity of the human organism and the limited conditions under which it can be observed, act as deterrents in many directions to the successful direct study of many of the diseases affecting it, and, therefore, to ascertain the general laws regulating them, workers have often been driven to employ lower and simpler animal forms. The reactions of the lower animal and the vegetable world even upon man's welfare are so numerous, and, indeed, often so subtle and essential, that it is only by obtaining the facts of their diseases that one may come to understand those of man himself. The newer pathology, therefore, embraces the study of the causes of disease, under as wide and varied conditions as may be, rather than the seats and processes of disease. Many of the greatest achievements of the present era in medical progress have come to us through the search for knowledge, which was not at once applicable to particular instances of disease, but which was entered upon partly for its own sake, partly as leading to a fuller understanding of biological processes in general. It will be my endeavor to review in a brief and cursory manner some of the problems confronting the newer pathology.

The prevention of disease, which in a proper system of medical science should precede the cure of disease, requires for its successful practice a knowledge of the mode of onset. In the case of the infective diseases, prevention depends, in large measure, upon mode of infection. Hence, it is necessary that we should possess knowledge of the manner in which microbes secure ingress into the body and, also, the way in which they leave the infected body. The portals of entry, as they are termed, have in the past been carefully defined, and out of the facts ascertained, certain repressive measures have grown. The knowledge, for example, of the infectiousness of dried and powdered tuberculous sputum and the even greater infectiousness of moist particles projected by the phthisical into the air by coughing, has led to the adoption of measures directed to the suppression of these dangers. The question of egress of the bacteria from the infected body has been emphasized more and more by reason of the occurrence in every large community of so-called microbe carriers. These unfortunate persons are often the innocent distributors of the germs of disease from which smaller and larger foci of infection arise. Fortunately for our welfare in the course of recovery from the infectious diseases the body employs mechanisms in disposing of germs which destroy them outright in considerable numbers and do not merely cast them outside the body. Only rarely do the bacteria which are within the body proper pass out of it in a condition to spread infection. But the case is quite different when the infective microörganism multiplies in those cavities of the body which are in direct communication with the exterior. The danger of the spread of diphtheria from infected persons to healthy ones, after full recovery from the disease has been attained, has long been recognized, and measures have been found out and adopted which have greatly minimized the dangers from this source. The case is far more serious in certain other diseases in which the microbe carriers play a sinister and less easily controlled part. Such carriers harbor the cholera vibrios, dysentery bacilli, influenza bacilli, plague bacilli, meningitis cocci, and typhoid bacilli. It is one of the problems of immediate importance to discover the means, first of detecting these carriers of disease germs, and next to remove the dangers arising from them by some measure which will not require the enforcement of any system of personal restraint upon the unhappy victims which might be unjust and intolerable. It is a happy circumstance that in the case of the majority of the germs mentioned the period of survival in healthy persons is brief and does not extend, possibly, beyond the duration of the epidemics from which they were derived. The facts regarding the typhoid bacilli and dysentery bacilli would appear to be different, since after longer periods, indeed after years in the case of the typhoid bacilli, they may still be eliminated in an active state. The typhoid bacilli become implanted in the intestinal canal, probably in that accessory organ to the intestine—the gall bladder—where they vegetate for years. The significance of this remarkable condition is only just being appreciated, and it will, doubtless, serve to explain many instances of mysterious so-called cryptogenetic-infection, through which smaller and larger groups of persons become attacked with typhoid fever.

For the effective application of preventive measures, experience has shown that man's animal associates and enemies must be carefully scrutinized. To remove all dangers of tuberculosis it will not suffice merely to suppress infection from man to man, but it is essential that the disease shall also be suppressed among cattle, and this, in spite of the possibility that they are only occasional sources of human infection. For the suppression in tropical countries of the bubonic plague it is essential that unremitting warfare be made upon the rat, which it would appear is the chief carrier of the infection. And in order to get rid of Malta fever it seems necessary to prohibit the sale and consumption of milk derived from Maltese goats, since these animals, it appears, secrete and harbor micrococcus melitensis for indefinite periods. But the problem, apparently, is much simpler as regards the spread of bacterial disease to man by means of domesticated and other animals that live in close association with him than it is with regard to the protozoan diseases in which the animal agency is far more potent. We are just beginning to learn the extent to which man and the lower animals are subjected to infection with protozoan parasites by the bite of the blood-sucking insects. The growth in number and in vital importance of the facts relating to the protozoan diseases of the higher animals justifies the faith which many pathologists and others reposed in investigation of this class of parasites. It is a matter of healthy national pride that in the discovery of the cause of Texas fever of cattle the foundation was laid for the development of knowledge of insect agency in transmitting disease germs, and in the successful artificial cultivation of trypanosoma the first pure cultures of parasitic protozoa were secured.

We are, however, still confronted with the problem of the causation of some of the most exquisitively infectious diseases — small-pox, yellow fever, scarlet fever, and measles — concerning the nature of the infecting germ we are in total ignorance. Now that we have come to know that there exists in nature a class of disease producing parasites so small as to be individually invisible even under the highest magnifying powers, it might be assumed — as, indeed, has been done — that it is among these minute organisms that the cause of these diseases are to be sought. The opportunities for discovery in this field are greatly reduced by reason of the fact that the diseases, small-pox exempted, are not transmissible to lower animals. On the other hand, it will be well to be chary of the assumption that because we are still ignorant of the infective germs of these diseases they must be ultra-microscopic in size. The very recent discovery of Spirocheta pallida, regarding which as the causative germ of syphilis the evidence becomes daily stronger, should make us cautious. The successful manner in which this organism, by no means ultra-microscopic, eluded detection for many years, in spite of the best zeal of some of the ablest investigators, should cause us to hesitate before assigning any size or form or special new property to an undiscovered microbe of disease.

Our knowledge of the pathology of syphilis had, until very recently, remained for a long period stationary. The discovery that the disease could be transmitted to anthrapoid apes and in a modified form to lower monkeys, and the still later observation that in the eyes of several different animals Spirocheta pallida multiplies and produces pathological changes associated with increase in virulence of the microörganism, and the discovery of the Spirocheta pallida itself, have led already and will lead still further to the accumulation of a rich body of facts regarding this destructive disease, which cannot help bringing results which may ameliorate its malignant consequences.

The rapidity with which a literature on the cause and inoculability upon lower animals has grown in the past three years since the new impulse was given to the study of syphilis, and the resulting large number of facts secured, may be taken as a measure of the scientific interest in etiological pathology and of the scientific efficiency diffused by it through the medical profession.

The task of pathology is merely rebegun by the discovery of the cause of any disease. To possess the cause is to be confronted with the problem of the immediate manner in which it acts upon the seats of disease to produce the changes which we recognize by the naked eye or through the microscope as being pathological, and with which certain clinical symptoms are correlated.

The time is entirely too brief for me to enter upon a detailed account of the many and illuminating facts which this direct study of the infectious agents of disease has yielded to pathology. Suffice it to say that the bacteria at least, and probably the protozoa also, bring about their injurious and peculiar effects, not because of any mechanical obstruction which they set up, or at most to a small extent by the operation of this effect, but by the elimination of poisons either as secretions or by reason of dissolution of their protoplasm. The sum of our knowledge regarding the activities of the parasites of disease is already very large and forms a new and remarkable chapter of toxicology. Many of the poisons secreted or yielded by the bacterial cells have been secured in considerable quantity from cultures and have been minutely studied. Thus far, however, no one has been obtained in an absolutely pure condition, although some of the purified products exhibit an almost marvelous degree of potency. With these products, as you know, or with the microörganisms themselves, animals may be immunized or rendered highly refractory to infection; and in several instances practical medicine has been enriched with new and valuable therapeutic agents in the form of antitoxic sera.

The studies upon immunity to bacterial infection has removed a large part of the mystery which surrounded the self-limiting diseases — so-called. Typhoid fever and the other bacterial infections have probably never been cured by medication. It has long been recognized by members of the medical profession that these diseases proceeded according to laws of which at most they could promote the workings, but which they could not set aside. It is, of course, true that medication does influence favorably some infectious diseases — of which it is necessary merely to refer to malaria and syphilis — but it should be added that malaria certainly and syphilis probably, or possibly, are protozoan diseases. The bacterial diseases would therefore appear to be subject to laws of cure somewhat different from the protozoan diseases. We know that coincident with recovery from bacterial diseases there appear in the fluids of the body certain new bodies — immunizing substances — often in considerable quantity. Doubtless the cure of bacterial disease is connected in some manner with the process through which these new bodies are evoked, or directly with the appearance of the new bodies themselves. There is evidence also at hand that in recovery from certain protozoan infections an immunity also appears. But we are just beginning to learn about this class of infections and we must wait patiently for the facts. The literature on immunity to bacterial disease is already voluminous and many facts of great value are contained in it.

Hardly any subject in biology possesses greater fascination for the curious-minded than the subject of immunity. The phenomena themselves are among the most marvelous adaptations in the whole range of biology. The part played by phagocytes in immunity cannot be doubted, although it still remains to define just what their limits of action are. The body fluids undoubtedly play a part also, as can no longer be denied. And we have begun to understand, in a measure, or to construct in our imagination, what the processes are through which these adaptations are produced. The phagocytic doctrine of immunity, as developed by Metchnikoff, and the humoral doctrine as promulgated by the German school and as illuminated by Ehrlich's brilliant hypotheses, have led to the acquisition of many new and valuable facts. It can excite neither wonder nor surprise to say that the whole of the immune state has not been explained by the sum of facts provided by the adherents of the two doctrines, and this quite irrespective of the phenomena which are still under dispute as being explained best by the one or the other. It is necessary only that we shall consider how imperfect is our knowledge of the relation between the development of immunity principles on the one hand, and the duration of the state of immunity on the other, to appreciate a part of the unsolved questions. Diphtheria and tetanus probably, when recovered from, lead to the accumulation of antitoxin in the blood; and this new substance can be used to immunize or to cure infection in small animals. Eventually the antitoxin disappears, and either because of this disappearance or for other reasons we know that an attack of diphtheria does not confer a lasting immunity. In the course of infection with the cholera vibrio immunity principles active in small animals develop in the blood, but their presence there is not an insurance against a subsequent attack of cholera. An attack of typhoid fever does, on the other hand, protect against subsequent attack, in spite of which the immunity principles present after the attack in the blood may have long ceased to be demonstrable.

The immunity in typhoid fever is not therefore a humoral immunity; and there is lack of convincing evidence that it is phagocytic in nature. The fixed cells of the body have been looked upon in the past as supplying immune bodies to the blood, but they have not been regarded especially as being active as centers or places of immunity reaction. Evidence is accumulating which would endow these cells with a considerable power of functioning as immunity organs, and not only in case of bacterial but also in case of toxin invasion. I deem it a forward step to have discovered in the fixed cells, once they have withstood successfully attack by bacteria, great sensitiveness of reaction to their presence. Such powers have been shown to be acquired by the endothelial cells of the serous cavities in experimental infection with the typhoid bacillus, and by the cells of the connective tissues in infection with tetanus bacilli, or poisoning with tetanus toxin. It has been suggested that the remarkable resistance displayed by our mucous membranes to many kinds of virulent bacteria arises from such local immunities and that the bacteria carriers who menace others but are themselves spared injury also possess special kinds of local immunities.

This field will be cultivated with profit in the future, and possibly one of the results achieved will be a better understanding of that perplexing question attending bactericidal immunity — the question of the relation of the immunity principles found in the blood to the totality of the immunity principles produced as results of bacterial infections. That some disparity exists would seem to be the necessary assumption in view of the considerable protective power which bactericidal sera exhibit for animals subjected to experimental infection as compared with man, the victim of a natural infection.

The high hopes entertained for serum therapeutics, based upon the marvelous activity of diphtheria antitoxin, have not, as you are aware, been realized. And yet it is a truth that, with few exceptions, all the bacterial diseases are infections in the real sense, and are not, as with diphtheria, an intoxication chiefly. Until we shall understand more fully the basis of acquired immunity in bacterial disease we can hardly hope to make great progress in preparing antisera for bacterial infections which shall rival antitoxin for diphtheria and tetanus. Perhaps this avenue of progress in the therapeutics of these diseases is permanently closed, as some profess to believe, because of the fundamental difference between toxin and endotoxin. But it is too soon to surrender the hope of preparing more actively bactericidal antisera using appropriate methods of immunization still to be discovered.

Into this chapter of bacterial disease there has just been cast a beam of hope by the proposal, made by Wright, to employ killed cultures of the infecting germs themselves as remedial agents. With such carefully standardized "vaccines" he believes that certain forms of infection can be influenced favorably in their course. Vaccination with weakened and dead cultures of bacteria is not a new or rediscovered method. Wright's great merit is that he applied it to the treatment and did not limit it to the prevention of disease. There is a kind of prescience in his having commanded the connective tissues, possibly the least profoundly and generally affected of all the tissues in infections, to assist in the fabrication of immunizing principles, not capable of ready transference from animal to animal, for the immediate and definitive use of a distant and diseased part of the same organism. And I hold the opinion that a real advance in the specific therapeutics of bacterial diseases may have been secured by this method which should, indeed, be unaffected by the fate that awaits the attempts at numerical estimation of the opsonic index of the blood.

A field of inquiry which promises to be highly fruitful is that of the ferments. The universal occurrence of ferments endowed with a multiplicity of activities in all the cells of the body can be taken to imply that they exercise important functions under pathological states of the body. The ferments of the different varieties of leucocytes have been partly, perhaps largely, revealed and the conditions of their activities ascertained. We are already, at this early day of their study, permitted to indulge the hope that we shall learn the manner in which their activities may be artificially influenced for the benefit of the organism. For just as in the bacterial infections, which constitute the self-limiting diseases, the mechanisms normally at the disposal of the body for overcoming the infective agent may fail unaided to accomplish a successful issue, so these ferments may also fall short of their wholesome intent.

Pathology has joined hands with experimental therapeutics in an endeavor to find new remedies for disease. Thus far the partnership has been limited to the study of the infectious diseases. Serum therapy, therapeutic vaccination, photodynamic anilines are part of the profits of this partnership. But the business of this young "corporation" has just begun and yet there are indications to be discerned that the profits will be considerable. Although I have not mentioned chemicals as being among the studies which engross pathologists, yet it is true that certain of them — quinine in malaria, mercury in syphilis — represent the purest examples of specific remedies we possess.

It seems highly improbable that these should remain the sole instances in nature of the specific action of chemicals in infectious disease. Indeed, as soon as the disinfectant action of chemicals upon pathogenic bacteria had been discovered, the hope was entertained that the more potent of them might act in the infected body as they were seen to do in the test-tube. The search for chemicals, which shall be as active upon parasites in the body as outside it, continues. The conditions of the quest are difficult; the chemicals must be only slightly noxious to the cells of the host and highly poisonous to the parasite. They must act in an albuminous fluid, such as the blood, as they do in water or salt solution. Expectation would have said that the second condition would be more easily fulfilled than the first; but experience has shown the reverse to be the case. Ehrlich has prepared a series of highly bactericidal chemicals which are relatively non-poisonous for the higher animals, but they are useless because they fix themselves to the proteid constituents of the lymph and blood and are rendered inactive upon the bacteria.

The beneficial action of chemicals in infections — in malaria and syphilis — is significant because recently still other diseases caused by protozoa — trypanosomic diseases chiefly — have been successfully combated by chemicals. The effects of trypan-red and trypan-blue — two aniline compounds — in curing artificial trypanosomiasis recall the earlier observations of Ehrlich on the successful treatment of malaria with methylene blue. Much the most brilliant results have been obtained by the use of arsenic — chiefly in that organic combination called atoxyl — in several forms of the natural and experimental infection with trypanosomes; and hopes are entertained that that murderous destroyer of man in Africa — sleeping-sickness — may even be arrested through its use. Ehrlich has just shown that even greater efficiency can be secured by administering in combination the effective anilines and arsenic compounds. A new impulse is thus given to the pursuit of therapeutics by these successes which furnish, also, a useful example of the practical value of experimental studies.

Until recent time no chapter in medicine has remained more obscure than that of the origin of tumors. Since Johannes Müller three-quarters of a century ago laid the foundation of pathological histology by the microscopical study of tumors, our advances consisted, first in a wider and more scientific classification, and next in a surgery of tumors which has indeed secured brilliant results. What advances in knowledge of the origin of tumors have come to us have been won, almost entirely, by the study of tumors occurring in the lower orders of animals, and chiefly by the discovery that certain tumors could be transplanted successfully from one animal to another of the same species. It will be admitted that far from the desired goal as we may still be and probably will remain for a long period of time, our horizon is being immensely enlarged by the studies of tumors in animals now being pursued with great energy and concentration in many places in the world. These investigations are yielding us gradually a store of facts of the life history — the biology — of tumors, which will be of the first importance in preparing the way for the more directly practical studies of the future. Had I the time I could, I think, not fail to interest you and even perhaps startle you with an account of certain remarkable and significant facts affecting the relations of host to tumor and tumor to host, which recent investigations have disclosed. Suffice it to say that by applying the principles gained in the study of infection and immunity in bacterial disease to the study of the transplantable tumors in mice, there has been at a stroke opened up wide vistas for future researches. No one would, I think, be justified in holding that because of similarity in the phenomena of bacterial and tumor immunity tumors are of necessity caused by parasites. What the phenomena really disclose is that infection and immunity to unicellular organisms are merely special cases of biological reactions applicable to a wider and more complex series of living structures, of which other special instances have been found in relation to hemolysins, cytotoxins, precipitins, agglutinins, and so on.

I must resist the inclination to carry you further afield into the problems of the newer pathology. If I have succeeded in any degree in making you feel that they constitute a promising field of human endeavor through which medical science and, through medical science, humanity may hope to benefit, I have accomplished my desire. I have aimed not alone to point out to you the fruits of past victories in this pathology but to give you a sense of the manner in which they have been won, so that you may better sympathize with the effect which will need to be put forth in the future in order that no backward step shall be taken, and that some progress may be made. Last of all would I wish to buoy your hopes that the practical problems of medicine, none of which I may add are new but all are as old as disease on earth, will be open to a direct attack now that knowledge long withheld from our predecessors is coming into our hands. You should reflect, rather, that every practical advance has been preceded by the acquisition of a knowledge in which the application could rarely be discerned. It is a hopeful sign, not a regrettable circumstance, that many men devote themselves to the acquisition of knowledge often for its own sake or to complete their views, hypothetical as they may be, of the nature of the phenomena that surround us.

In modern times the world has not produced a greater benefactor to the human race than Louis Pasteur. It was in Lille that the studies on fermentation were begun. What those studies have come to mean you all know. Let me, therefore, quote from a lecture to his students with which he began his teaching and in which he expressed the inspiration of his work: "Without theory, practice is but routine born of habit. Theory alone can bring forth and develop the spirit of invention. It is to you specially that it will belong not to share the opinion of those narrow minds who disdain everything in science which has not an immediate application. You know Franklin's charming saying? He was witnessing the first demonstration of a purely scientific discovery and people around him said: 'But what is the use of it?' Franklin answered them: 'What is the use of a new-born child?' Yes, gentlemen, what is the use of a new-born child? And yet perhaps at that tender age, germs already existed in you of talents which distinguish you. . . . And thus, gentlemen, a theoretical discovery has but the merit of its existence; it awakens hope, that is all. But let it be cultivated, and you will see what it will become."

TOAST:

TO THE SURVIVING MEMBERS OF THE PATHOLOGICAL SOCIETY.

S. WEIR MITCHELL, M.D.

I am I presume the oldest save one of the notable men who in 1857 founded the Pathological Society. I see in your volume of reports that I presented the first specimen, a case of fatty liver in a child.

The few surviving members of this Society are fast nearing the deadly rifle pits of life's limit, but there are those still left whose friendship neither time nor any incident of life has lessened. Among these I like to name for my personal pleasure the accomplished physician and botanist, James Darrach, one of the most active of our early members; John Packard, in whom a charming artist added skill to a surgeon's career. I regret not to see here William Moss, of Chestnut Hill, an army surgeon of distinction who, in the days of the great war, when courage was too usual to excite remark, was spoken of as brave beyond the common. Dr. Harlan sends me a survivor's smile, and I turn from the living to grieve over my latest loss, and yours, John H. Brinton, a man to be missed in every relation of life; the staff surgeon and friend of Grant, Sherman, and Sheridan; and the creator and Curator of the great Pathological Museum of Washington.

May I not linger to leave the laurel of achievement on the remembered graves of DaCosta, Agnew, the Grosses, and others. But I am yet to tax your patience, and I have suffered too much from the confident eloquence of the after-dinner hour not to have learned the lesson of charitable forbearance.

This Society owed much to war. Brinton, Moss, Woodward, and Keen were in the regular service. Some forty of our members served as acting surgeons. I think we used well the terrible opportunities of those bloody sixties, and if you are to-day as enthusiastic, as industrious, and as fertile, you are to be congratulated. I do not mean, however, to leave you without gayer remembrances of my presence.

Some years ago I read at a college dinner some light verses. I gave away no copies. They were never reported. They are fair pathologic nonsense, and as I am asked for poetry and can at this season only offer verse — my Muse cannot endure winter weather — I have rewritten these lines for you. I could wish them better and less open to critical therapeutics, but if perfect they would lack pathological quality, and be therefore quite out of place.

(Lines read at the Dinner to commemorate the Fiftieth Anniversary of the Pathological Society of Philadelphia.)

Take then my friends or old or new in charitable mood,
The best I have or good or bad, whate'er my fancy brewed.
They used to soak their old time toasts, I hope you're soaking mine;
Prosperity attends the toast that's duly soaked in wine.
To-day's gay memories recall the young and strong who met
A half a century ago, ere time its mark had set
In furrowed wrinkles on the brows where soon the plough of life
Left traces of the scholar's toil, and of a nation's strife.
How thinned alas those sturdy ranks! But still your record shows
The honored work of men whose thought each living language knows.
God rest the friends long passed away, the earnest, learned, and true,
Whose fertile manhood many a year your early annals knew,
No gayer comrades winged the jest across the festal board,
No keener broke the lance of thought. For them, with joy be poured
The wine of memory's golden day. Perchance on us they look
And taste the wine, and laugh unheard, and wonder why some book
They wrote at cost of weary hours wins never now a look.
So Fate will mock us, too, in turn.
I paused. "Sir, Order there!
Is this your notion, Sir, of jests?" is whispered by the chair.
"Your time is getting very short and sundry noted wits
Are waiting quite impatiently with effervescent hits:
These long-kept jokes will decompose and need a disinfectant;
And men do say you're rather prone to medicine expectant."
I paused, my old asthmatic Muse had stopped to loose her stays,
Or pull her garters up, Lord knows! she has immodest ways.
I paused, 'twas after dinner — I may have slept it seems,
And won some merry fancy from the Muse who brings us dreams.
Accept the consequences, I saw this table dressed
The living merry o'er their wine and many a ghostly guest.
In came the Secretary, sir, serene as fits his station;
He said, "A stranger waits without. He wants a consultation.

His malady is chronic, or so he is assured,
He says — I can't believe him — that it never can be cured.
He says he wants no nonsense, Sir, with just one man or two,
He wants a hundred specialists to tell him what to do."
"Go fetch him in," the Chairman cried, "Get every man his books."
The surgeons dropped their forks and spoons and sharpened up their looks,
The ologists and cologists got out their phones and scopes,
Those wild illuminati with their incandescent hopes.

He was a very ancient man. He wore a third rate cloak,
He coughed a little wheezy cough; he trembled as he spoke.
The Secretary asked his age. His memory was not good:
The family Bible, so he said, was lost about the Flood.
They left him lonesome on a log when Noah sailed away,
Because there were not two of him! What could a fellow say?
He said it was quite damp outside. He felt it to this day.
He laid his hat upon the floor. He turned an hour-glass tall.
He set his scythe upon a chair and leaned against the wall.
He said, "I've got but half an hour and that must do for all."

What happened then I dimly saw; no doubt your minutes tell.
A great variety of things that hapless wight befell.
A younger doctor rose elate. He cried, "I have a treatise
Which shows that all our human ills are just appendicitis."
The Chairman roared, "Appendix! Stuff! His table of errata
I do suppose more fitly shows the pathologic data."
A surgeon cried, "How simple is the art of diagnosis
Just open all the cavities in place of vague supposes."
Arose a gynecologist — "Why all this silly fuss!
What inconsiderate fellow fetched this inappropriate cuss?"
They fell upon that ancient man, they took his stomach out,
His floating kidneys gone adrift were handed round about.
And then they said reflectively, "Now find him a physician —
To follow on the surgeon's knife should be his only mission.
We do not doubt they'll fetch him out with still a little future;"
And so at last they sewed him up with a fine cat's cradle suture.
Rose then a grim neurologist with glasses on his nose,
"Neurasthenia-chirurgica, his case is, I suppose."
"I wish, Sir," cried a doctor, "I wish, Sir, to protest.
His lights are out, his spleen is gone, there's little left at best.
And by and by the surgeons, who blunder to our aid,
Will leave the sad pathologist not one unguessed charade.
There can be no diagnosis unless the man is dead —
Till then 'tis mere agnosis and there's no more to be said."

About this time the patient beginning to revive,
Observed an ardent surgeon disinfecting of his scythe.
He contemplated woefully his relics round about.
He said his chronic malady did still remain in doubt,
It could not be organic with all the organs out.

"I thank you, gentlemen," he said, "but now I must be going."
On this the Chairman sweetly smiled; his look was very knowing.
He laid that hour-glass on its side. The patient leaped aghast.
"The sands are stopped. You've done for both the future and the past."
Remorseful younger doctors wailed: "This thing did none intend,
There will be no resignations if Time is at an end."
An old professor smiled and cried, "I guess we've won the trick;"
The hands on all the watches struck; the clocks could get no tick.
The very trains got in on time; the almanac fell sick
And on the floor that patient lay and saw with failing powers
The Chairman stand, like Joshua, and mix the addled hours.
Then in the doorway, lo, I saw a stolid man and fat;
A constable was he and wore a disrespectful hat.
Says he, "I always like a cove as is inclined to rhyme,
But this has gone, Sir, quite too far. You've been a' killing Time."
Thereon the doctors all rose up, both surgeons and M.D.'s,
Neurologists and ologists and specialities.
They cried, "We have been killing Time; we'll kill him when we please!
And if you don't get up and leave, blue-coated cop and fistic,
We'll set on you some man who is bacteriologistic."
That cop he gave a howl of fear. He fled as you will run
The next time, Sir, I undertake to make a bit of fun.

TUBERCULOUS INFECTION THROUGH THE ALIMENTARY CANAL.*

Mazÿck P. Ravenel, M.D., and John Reichel, V.M.D.
(*From the Laboratory of the State Live Stock Sanitary Board of Pennsylvania.*)

Since the demonstration of the communicability of tuberculosis by Villemin much work both from an experimental and statistical standpoint has been conducted to determine the mode of infection or entrance of the tubercle bacillus into the body of the host. That it is possible for infection to take place through the digestive tract was first pointed out by Klenke in 1846; he gave the clinical histories of sixteen children who had been nourished on cows' milk, all of whom showed tuberculous lesions of the intestines, glands, skin or bones. While his observations lacked scientific exactness, he deserves credit for having called attention to a method of infection which recent research has shown to be of quite frequent occurrence.

The first experiments published proving the possibility of tuberculous infection through the alimentary canal were reported by Chauveau in 1868. He employed for this purpose young cattle, reared in a district where tuberculosis was practically unknown. Further successful experiments carried out on a larger number of animals were reported by him in 1872 and 1873, establishing at this early date, for cattle at least, the important part played by ingestion in the transmission of tuberculosis.

The work of Chauveau received strong support in the experiments of Gerlach begun in Hanover in 1866 and later continued in Berlin on a much larger scale. Gerlach was the first to experiment with the milk of tuberculous cows and to prove that animals could be infected by the ingestion of such milk.

Villemin in 1869 published the results of experiments carried out on rabbits and guinea-pigs, in which he caused

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infection by introducing tuberculous material into the stomach by the use of a tube.

In 1870 E. Klebs reported experiments in which he had produced tuberculosis in animals by feeding tuberculous material from man as well as from animals, showing thereby the identity of the diseases. In 1873 he extended his experiments, and employed tuberculous milk with positive results.

During the years 1870–1873 Günther and Harms, at Hanover, conducted ninety-four feeding experiments, using various animals of widely different species and tuberculous material of various kinds. They obtained twenty-four positive and seventy negative or doubtful results.

The admirable work of Viseur, Bollinger, Colin, Semmer, Orth, Toussaint, Peuch, Baumgarten, Wesener, Leisering, Zürn, Virchow and Schutz, Sidney-Martin, Pearson, Mohler, Schottelius, Schroeder, and others, all showing that tuberculous infection takes place readily through the alimentary tract, cannot be gone into in detail.

Many other facts, some experimental, some accidental, are at hand confirmatory of the results above quoted. Among those may be mentioned the infection of large numbers of swine through feeding milk from tuberculous cattle, skimmed milk, and the waste products of creameries, and through eating the feces of tuberculous cattle, tuberculous infection from these sources being a well-established fact.

In 1901 Koch, in his memorable London address, discussing the relation of bovine tuberculosis to human tuberculosis, held that infection through the alimentary tract occurred but rarely and should not be considered of much more importance as a mode of infection than hereditary transmission. This statement he made upon the basis of observations on autopsies, which he claimed showed that a primary tuberculous lesion in the alimentary tract was extremely rare, taking it for granted that the tubercle bacillus was unable to gain entrance to the system through the intestinal wall without the production of a lesion at the point of entrance.

It has been thoroughly proven that the tubercle bacillus is able to penetrate the mucous membrane of practically the entire alimentary canal as well as that of various other parts of the body. Experiments demonstrating this will be quoted when considering the various portions of the alimentary tract which may serve as portals of entry.

Mouth and tongue, palate and gums. — Tuberculosis of these structures is rare, even as a secondary manifestation in advanced cases of tuberculosis, when all the parts are constantly exposed to large quantities of sputum containing myriads of tubercle bacilli. Experimental infection is readily produced followed by enlargement and caseation of the related glands, but as a primary avenue of entrance they play a minor part in the spread of tuberculosis.

Tonsils. — The tonsils have long been believed to serve as portals of entry, not only for the tubercle bacillus, but also for many other pathogenic microörganisms. They are not infrequently the seat of primary tuberculosis and often show scars and other changes attributable to tuberculosis. In man they are so situated as to come into contact readily with food as it is swallowed. They are also exposed to the secretions of the nose and naso-pharynx, as it passes backward into the esophagus, hence are liable to infection from food as well as from material primarily lodging in the nose.

The literature concerning infection through the tonsils is extensive, and of great value. In the examination of tonsils removed from otherwise healthy persons Krückmann found primary tuberculosis in two of twenty-five cases, Gottstein in two of twenty, Pluder and Fischer in five of thirty-two, and Scheibner in four of sixty cases. Wood has collected from the literature one thousand six hundred and seventy-one cases, eighty-eight of which (5.2 per cent) showed primary tuberculosis. These examinations were made by various methods and probably fall short of the truth. The susceptibility of the tonsils to tuberculous infection is shown by the examination of persons dead of phthisis, and additional evidence is found in the statistics obtained at our slaughter-houses where tuberculous lesions are frequently found in the tonsils, particularly in swine.

Experimentally, the tonsils are readily infected by direct application, as well as by feeding tuberculous material. In a series of experiments carried out at the laboratory of the State Live Stock Sanitary Board of Pennsylvania, swine fed tubercle bacilli from man and from cattle developed generalized tuberculosis, with marked involvement of the tonsils, apparently primary, ending in necrosis and ulceration. Baumgarten observed in his feeding experiments in 1884 that his animals showed primary tonsillar tuberculosis with involvement of the related glands, and the same course was noted also by Orth in his studies.

Woodhead traced tubèrculous infection in swine from the tonsils into the neck, then into the thorax by the mediastinal and post-sternal glands.

Peira has shown that microörganisms are absorbed through the tonsillar epithelium and, if virulent, may cause not only local disease, but be carried to the neighboring lymphatics and thence to different parts of the body. Lexer confirmed these observations by a series of experiments on rabbits.

Wood in researches made in the laboratory of the Pennsylvania State Live Stock Sanitary Board found that in swine applications of tubercle bacilli to the back of the mouth produced rapidly a primary tuberculosis of the tonsils, followed promptly by involvement of the submaxillary and cervical glands and extensive disease of the lungs. The mesenteric and bronchial glands were always diseased in about an equal degree.

Aufrecht, by rubbing cheesy matter into the tonsillar region of rabbits, produced in one tuberculosis of the right tonsil and root of the tongue; in a second, tuberculosis of the cervical and mediastinal glands and lung; in a third, disease of the mediastinal glands and lung. All other organs remained free.

Grober concludes from his thorough study of the question that infection through the tonsil is the most frequent origin of apical tuberculosis. His experiments have demonstrated that from the cervical glands there is a direct route to the pleuræ and lungs and that this leads especially to that portion of the lung most frequently the primary seat of tuberculosis — the apex.

The evidence that the tonsils are frequently the portal of entry for the tubercle bacillus appears to be conclusive.

Pharynx and esophagus. — Tuberculosis of the pharynx and esophagus is extremely rare and primary infection is practically unknown. It is probable, however, that the intact mucous membrane of the pharynx at times allows the passage of tubercle bacilli which first show their presence by enlargement of the related glands. Experimental indications of this are strong, though it must be borne in mind that it is always difficult to place the exact point of entry in the absence of any lesion.

Stomach. — There is no evidence that infection ever takes place through the stomach. Tuberculous disease of this organ is one of the rarest lesions seen. The cause of this apparent immunity is not evident, but it is attributed to the protective action of the hydrochloric acid of the gastric juice. The action of the gastric juice on the tubercle bacillus has been the subject of considerable discussion and experiment. If this fluid had a germicidal effect on the tubercle bacillus, primary infection through the intestines would be manifestly impossible. It has been shown, however, that it is able to resist the action of the gastric juice for at least as long as the ordinary period of digestion.

Intestine. — The intestine is very frequently involved in cases of pulmonary tuberculosis. In the great majority of cases the lesions found are unquestionably secondary and due to swallowing sputum laden with tubercle bacilli. Though it be true that lesions that may be recognized as primary tuberculosis are comparatively rare, this does not preclude the possibility that the pulmonary tuberculosis was caused in the first place by tubercle bacilli which gained entrance to the body through the intestine. In other words, the location of what may be demonstrated as a primary lesion, on which so much stress has been laid, does not indicate with certainty the point of entrance of the invading organism.

This appears to be especially true in children, in whom tuberculosis tends to become rapidly generalized.

The susceptibility to infection through the intestines unquestionably varies with the age of the individual. In young children the intestinal epithelium is looser, more delicate and softer than in later life, the mucous membrane contains more fluid and is more liable to slight injury (Furst). This, without doubt, holds true also for young animals. Even before the discovery of the tubercle bacillus Weigert called attention to the permeability of the intestinal mucosa of young children to the virus of tuberculosis, stating that the mesenteric glands might' be markedly swollen and cheesy, while the mucosa and lymph vessels showed no change whatever.

Tuberculosis of the mesenteric glands without lesions of the intestinal mucosa was observed also by Cohnheim and since by von Bollinger, Wesener, Heller, Kossel, Aufrecht, von Hansemann, Rilliet and Barthez, Widerhofer, and many others.

Primary intestinal tuberculosis has been studied by pathologists almost entirely from autopsies upon the human body, and their reports as to its frequency differ widely, which is probably accounted for, in part, by difference in the method of examination and interpretation of findings; in part by the class of patients frequenting certain hospitals, and in part by a real difference in the incidence of intestinal infection in various communities brought about by local habits and by the extent of infection of the milk and meat supply.

Hof in a systematic study of the autopsy records of the Pathological Institute at Kiel found two thousand six hundred and ninety-seven cases of tuberculosis in adults; one hundred and fifty-nine (5.9 per cent) of which were primarily in the intestine, while in 84.9 per cent the respiratory tract was primarily involved. In children there were nine hundred and thirty-six cases of tuberculosis, two hundred and thirty-five (25.1 per cent) of which showed evidence of infection through the intestine and five hundred and twenty-seven (56.2 per cent) respiratory infection. Hueppe, while giving no statistics, says: "The number of cases (primary intestinal tuberculosis) may fairly be reckoned as between twenty-five and thirty-five per cent of all deaths in children of tuberculosis."

Wagener, in six hundred autopsies, seventy-six of which were children, found primary intestinal tuberculosis in sixteen to twenty-one per cent. Heller, among seven hundred and fourteen fatal cases of diphtheria, found tuberculosis one hundred and forty times, in fifty-three (37 per cent) of which the origin was primary in the intestine. In a later series of autopsies Heller found intestinal tuberculosis in twelve per cent of the adults and twenty-six per cent of the children.

Studies on the bodies of children who have died of other diseases than tuberculosis, such as those reported by Councilman, Mallory and Pearce, Heller, and Kossel are particularly valuable in the determination of the avenue of entry of the tubercle bacillus. The disease tends to become generalized so rapidly in children that at autopsy it is often impossible to tell by what route infection occurred. When death has been due to other causes, the tuberculous lesion is usually localized and often confined to the glands in relation to the point of invasion, hence the portal of entry can be determined with greater certainty.

Recent experiments have shown that it is unfair to consider as cases of intestinal infection only those in which the primary lesion is found in the intestine or mesenteric glands. The question hinges largely on the ability of the tubercle bacillus to pass through the intestinal wall without causing a lesion at the point of entrance and this will be next considered.

Permeability of the intestinal wall. — It is believed by many pathologists that the tubercle bacillus is able to penetrate the normal mucous membrane of the intestine without leaving any lesion at the point of entrance. In fact this seems to be true of the mucous membrane of other parts of the body also, as shown by the great frequency with which the various groups of glands are found to be tuberculous with no demonstrable lesion of the surfaces they drain. In one thousand swine, infected through food, as reported by Ostertag, the glands of the throat, neck, and mesentery were tuberculous, while the mucous membrane of the intestines was always free from disease. The passage of tubercle bacilli through the intestine appears to be most liable to occur during the digestion of fats, as shown in experiments given below.

Von Baumgarten has recently denied that tubercle bacilli penetrate the body membranes without causing a lesion at the point of entry. In the numerous experiments by himself and his students he has found that animals fed with milk containing tubercle bacilli develop an intestinal tuberculosis with general infection. If the infection was rapidly fatal the intestinal lesions were very small, being found only in histological sections, but widespread. The mesenteric glands showed more advanced disease and apparently of longer duration.

Von Hansemann accounts for cases of abdominal infection without intestinal lesion on the ground that a slight tuberculosis of the intestines may disappear leaving no sign of its location. The truth of this observation must be admitted, but it does not explain the numerous experiments in which the tubercle bacillus as well as other organisms have been shown to penetrate the intestinal wall in the course of a few hours even when there is no demonstrable lesion.

Dobroklonski in 1890, working under Cornil, showed that the tubercle bacillus would quickly penetrate the healthy wall of the intestines in guinea-pigs. Desoubry and Porcher, students of Nocard, showed that in dogs during the digestion of fats large numbers of bacteria were carried through the intestinal wall and could be detected in the chyle within a few hours after the meal was given. If food free from fat was given, few or even no bacteria could be found. Nicolas and Descos, 1902, found that tubercle bacilli given to dogs in fatty food reached the chyle within three hours. During feeding experiments conducted at the laboratory of the State Live Stock Sanitary Board of Pennsylvania, extensive tuberculosis of the lungs and thoracic glands in animals which showed slight or even no involvement of the intestine was observed. In 1902–3 Ravenel introduced into the stomach of a number of dogs tubercle bacilli suspended in an emulsion of melted butter and warm water, using a tube in order to prevent possible infection through the tonsils and trachea. The dogs were killed after three and one-half to four hours during active digestion, as much chyle collected as possible and the mesenteric glands removed. Guinea-pigs were inoculated with this material and the presence of tubercle bacilli was demonstrated in eight of ten experiments. The dogs were kept on soft food for some days before the experiments and purged with castor-oil, in order to rid the intestine of all foreign matter which might have injured the mucous membrane. Numerous sections of the gut were examined also but no injury could be detected. Römer and von Behring have shown that the tubercle bacillus, and even the anthrax bacillus, which is very much larger, passes rapidly through the intestinal mucosa of young guinea-pigs. A single feeding produced infection, the glands of the neck always being involved, and later these frequently developed a type of disease usually regarded as the expression of an inhalation tuberculosis. As is well known, von Behring believes that the origin of epidemiological pulmonary tuberculosis in man and epizoötic pulmonary tuberculosis in cattle is a primary intestinal infection taking place in early life.

This subject has been recently studied by Calmette and his fellow workers, Guérin, Vansteenberghe, and Grysez. In numerous experiments they have found it impossible to produce anthracosis of the lungs even when animals were compelled to breathe an atmosphere saturated with lamp black, provided the esophagus was closed. On the other hand, when lamp black was introduced into the stomach by means of a tube, or mixed with food, anthracosis of the lungs appeared rapidly. When tubercle bacilli, dry or moist, were administered by inhalation, by intratracheal insufflation or direct inoculation into the trachea, the bacilli never penetrated further than the first branches of the bronchi. The introduction of tubercle bacilli into the stomach through a tube, in order to avoid danger of respiratory infection, always produced tuberculosis rapidly. They confirm the observation that tubercle bacilli readily penetrate the intestinal wall without leaving a lesion. They have traced the bacilli and find that as soon as they reach the chyle vessels they are taken up by the leucocytes, which from this time act as carriers and convey them to the related glands, where they are retained for a longer or shorter time, reaching finally the thoracic duct and through it the circulation. In young animals the mesenteric glands retain the leucocytes with their englobed bacilli for some time, the glands enlarging in proportion to the intensity of the infection, the lungs becoming involved secondarily. In the adult the glands do not retain the bacilli nearly so long, and they can be detected in the lungs twenty-four hours after their introduction into the stomach. Calmette concludes that pulmonary tuberculosis acquired at any age may be due to recent intestinal infection.

Besanti and Panisset have shown that tubercle bacilli suspended in soup given to dogs reach the blood of the heart within four or five hours. In four out of five experiments they obtained positive results. Bartel found that a single dose of tubercle bacilli penetrated the uninjured intestine and reached the mesenteric glands during the following digestive period. Von Weismayer, as the result of his studies, is of the opinion that microörganisms can penetrate the intact intestinal wall and be carried by the lymph cells through the lymph channels to the related glands.

Schlossmann and Engel have shown that when tubercle bacilli suspended in milk or cream are injected into the stomach of young guinea-pigs through an incision in the abdominal wall they reach the lungs within six hours, as shown by killing the animal and inoculating the lungs into other pigs.

As is seen, much work is being done to obtain experimental proof upon this subject and this has led the writers to take up the following piece of work, which must be regarded as but one of a series of experiments along this line.

Problems of the experiment. — (1) To determine the ability of tubercle bacilli to pass through the intestinal wall of healthy guinea-pigs. (2) The time required for them to reach the lungs.

As to the general method of the experiment it may be said that the work of Schlossmann and Engel was in mind when this work was started. We wished to test their results and drew from their original plan, which in a general way was closely followed. Young guinea-pigs were used which had been deprived of food for some hours before they were operated upon. The guinea-pig was etherized and placed on its back, a little inclined to its right side; the hair was clipped from the abdomen and the left side, and the parts thoroughly cleansed. An incision was made through the skin one-half to three-quarters of an inch long, parallel to the last rib, starting about one-half inch from the sternal cartilage and one-sixth of an inch posterior to the last rib. The incision was then extended through the muscular coat and peritoneum, which usually exposed the anterior face of the liver. With a pair of small smooth-pointed forceps the edge of the liver was pushed upward, the stomach grasped and raised partially through the incision.

An emulsion of tubercle bacilli of known virulence for guinea-pigs, rabbits, and cattle was used, made up in normal salt solution so that each cubic centimeter contained five hundred milligrams of tubercle bacilli. One volume of this emulsion was mixed with an equal volume of fresh heavy cream. Of this emulsion of tubercle bacilli in cream, each guinea-pig received two cubic centimeters or more, directly into the stomach. An extremely fine hypodermic needle was used. The needle was plunged into petrolatum, kept hard by cold, before it was attached to the filled syringe. The petrolatum plugged the needle sufficiently to prevent the escape of any of the emulsion during the insertion of the needle into the stomach. The petrolatum that clung to the outside of the needle formed a ring around the needle when inserted into the stomach, which we hoped would serve as a protective on withdrawing. On withdrawing the needle the stomach was supported by a pledget of cotton wet with bichloride of mercury solution (1–1000) pinched about the needle. The stomach was then carefully wiped off with the same solution and returned to the abdominal cavity.

Leakage was carefully looked for both at the time of inoculation, and also when the animal was killed. We satisfied ourselves that none could take place by trying to force the emulsion through the puncture in several pigs which died from the effects of ether. In no case could we detect even the smallest quantity.

Sixty-five guinea-pigs were operated upon and inoculated in this manner, of which ten were permitted to live for six weeks as controls and then chloroformed. Of the others, ten were chloroformed after four hours, twelve after five hours, eight after six hours and the remainder were permitted to live for different periods, the longest being twenty-four hours.

The lungs from each guinea-pig were removed by raising one lobe at a time and cutting off close to the root. The lung tissue was ground in a mortar with physiological salt solution and injected intraperitoneally into a pair of healthy guinea-pigs.

In the following tables (Nos. I., II., and III.) the guinea-pigs inoculated in the stomach are described in the first four columns. The following columns relate to the guinea-pigs inoculated with lung tissue from the first mentioned. The last column shows whether lesions of tuberculosis resulted from such sub-inoculation.

TABLE NO. I.

Shows results of inoculations directly into the stomach, the guinea-pig killed in four (4) hours and a healthy pair of guinea-pigs inoculated with the lungs of the first guinea-pig.

G.P. No.	Weight of G.P. (Grams.)	Age of G.P.	Permitted to Live.	G.P. Inoculated.	T.B. or T.F.	Omentum.	Spleen.	Liver.	Lung.	Positive or Negative.
1071. No. VII.	111	20 hrs.	4 hrs.	1072. No. V. 1072. No. VI.	T.B. T.B.	× × × × ×	× × × ×	…… ……	…… ……	Positive.
1071. No. IV.	90	37 hrs.	4 hrs.	1072. No. III. 1072. No. IV.	T.F. T.B.	…… × ×	…… ……	…… ……	…… ……	Positive.
1071 No. I.	91	55 hrs.	4 hrs.	1072. No. I. 1072. No. II.	T.F. T.B.	…… × ×	…… ×	…… ……	…… ……	Positive.
1077. No. VI.	100	90 hrs.	4 hrs.	1075. No. I. 1075. No. II.	T.B. T.B.	× × × × × ×	× × × × × ×	× × × ×	…… ……	Positive.
1060. No. V.	120	⊕	4 hrs.	1070. No. VII. 1070. No. VIII.	T.B. T.B.	× × × × × ×	× × × × × ×	× × × ×	…… × ×	Positive.
1060. No. IV.	130	⊕	4 hrs.	1070. No. V. 1070. No. VI.	T.F. T.F.	…… ……	…… ……	…… ……	…… ……	Negative.
1030. No. I.	250	⊕	4 hrs.	1040. No. I. 1040. No. II.	T.F. T.F.	…… ……	…… ……	…… ……	…… ……	Negative.
1030. No. II.	205	⊕	4 hrs.	1041. No. I. 1041. No. II.	T.B. T.F.	× × ……	× × ……	…… ……	× ……	Positive.

× signifies extent of tuberculous lesions.
⊕ signifies age of guinea-pig, seven days or more.
T.B. signifies tubercle bacilli present, as shown by result of inoculations.
T.F. signifies tuberculosis free, as shown by inoculations.

TABLE No. II.

Shows results of inoculations directly into the stomach, the guinea-pig killed in five (5) hours and a healthy pair of guinea-pigs inoculated with the lungs from the first guinea-pig.

G.P. No.	Weight of G.P. (Grams.)	Age of G.P.	Permitted to Live.	G.P. Inoculated.	T.B. or T.F.	Omentum.	Spleen.†	Liver.	Lungs.	Positive or Negative.
1071. No. X.	68	16 hrs.	5 hrs.	1073. No III. 1073. No. IV.	T.F. T.B.	.... × ×	.... × ×	.... × ×	.... × ×	Positive.
1071. No. XII.	80	16 hrs.	5 hrs.	1073. No. IX. 1073. No. X.	T.B. T.B.	× × × ×	× × × ×	× ×	× × ×	Positive.
1044. No. II.........	88	72 hrs.	5 hrs.	1045. No. I. 1045. No. II.	T.B. T.B.	.... × ×	.... × × ×	....	....	Positive.
1044. No. III..........	88	72 hrs.	5 hrs.	1046. No. I. 1046. No. II.	T.F. T.F.	....	....	....	....	Negative.
1077. No. VIII.........	93	96 hrs.	5 hrs.	1075. No. III. 1075. No. IV.	T.F. T.F.	....	....	....	....	Negative.
1071. No. VIII.........	94	....	5 hrs.	1072. No. IX. 1072. No. X.	T.B. T.B.	×	× × × × ×	× ×	....	Positive.
1069. No. III...........	150	(†)	5 hrs.	1070. No. III. 1070. No. IV.	T.B. T.F.	×	×	....	....	Positive.
1069. No. II............	100	(†)	5 hrs.	1070. No. I. 1070. No. II.	T.F. T.F.	....	....	....	....	Negative.
1062. No. II...........	200	(†)	5 hrs.	1063. No. I. 1063. No. II.	T.F. T.F.	....	....	....	....	Negative.
1062. No. VI...........	210	(†)	5 hrs.	1066. No. I. 1066. No. II.	T.F. T.F.	....	....	....	....	Negative.
1062. No. IV...........	220	(†)	5 hrs.	1064. No. I. 1064. No. II.	T.F. T.F.	....	....	....	....	Negative.
1062. No. III...........	230	(†)	5 hrs.	1064. No. I. 1064. No. II.	T.B. T.B.	× × × ×	× × ×	× ×	.... ×	Positive.

× signifies extent of tuberculous lesions.
(†) signifies age of guinea pig, seven days or more.
T.B. signifies tubercle bacilli present, as shown by results of inoculations.
T.F. signifies tuberculosis free, as shown by inoculations.

TABLE NO. III.

Shows results of inoculations directly into the stomach, the guinea-pig killed in six (6) hours and a healthy pair of guinea-pigs inoculated with the lungs from the first guinea-pig.

G.P. No.	Weight of G.P. (Grams.)	Age of G.P.	Permitted to Live.	G.P. Inoculated.	T.B. or T.F.	Omentum.	Spleen.	Liver.	Lung.	Positive or Negative.
1071. No. VI.	82	37 hrs.	6 hrs.	1073. No. I.	T.F.	....	....	....	....	Negative.
1071. No. III.	100	55 hrs.	6 hrs.	1072. No. VII.	T.B.	× ×	× × ×	....	....	Positive.
				1072. No. VIII.	T.B.	× ×	× ×	× ×	× ×	
1071. No. XI.	90	21 hrs.	6 hrs.	1073. No. VII.	T.F.	....	....	....	....	Positive.
				1073. No. VIII.	T.B.	× ×	× ×	....	....	
1071. No. IX.	95	20 hrs.	6 hrs.	1073. No. V.	T.B.	× ×	× ×	× ×	....	Positive.
				1073. No. VI.	T.B.	× ×	× ×	....	....	
1077. No. V.	74	70 hrs.	6 hrs.	1075. No. V.	T.F.	....	....	....	....	Negative.
				1075. No. VI.	T.F.	....	....	....	....	
1077. No. VIII.	97	90 hrs.	6 hrs.	1075. No. VII.	T.B.	× ×	× ×	....	....	Positive.
				1075. No. VIII.	T.B.	× ×	× × ×	× ×	....	
1047. No. V.	150	⊕	6 hrs.	1051. No. I.	T.F.	....	....	....	....	Negative.
				1051. No. II.	T.F.	....	....	....	....	
1047. No. IV.	230	⊕	6 hrs.	1050. No. I.	T.F.	....	....	....	....	Negative
				1050. No. II.	T.F.	....	....	....	....	
1047. No. II.	240	⊕	6 hrs.	1048. No. I.	T.F.	....	....	....	....	Negative.
				1048. No. II.	T.F.	....	....	....	....	
1047. No. III.	290	⊕	6 hrs.	1049. No. I.	T.F.	....	....	....	....	Negative.
				1049. No. II.	T.F.	....	....	....	....	

× signifies extent of tuberculous lesions.
⊕ signifies age of guinea-pig, seven days or more.
T.B. signifies tubercle bacilli present, as shown by result of inoculations.
T.F. signifies tuberculosis free, as shown by inoculations.

As shown by the above three tables, thirty guinea-pigs from sixteen hours to two weeks of age were inoculated directly into the stomach, killed in four, five, and six hours after inoculation, and healthy guinea-pigs inoculated intraperitoneally with their lungs. Of the thirty pairs, sixteen pairs showed that the emulsion of lung tissue with which they had been inoculated contained tubercle bacilli, since tuberculous lesions were found in one or both of the pigs when chloroformed six weeks after inoculation. Fourteen pairs showed no lesion, showing that the emulsion of lung tissue was free from tubercle bacilli.

In studying the three tables, it will be noticed that positive results were most frequent in the guinea-pigs sixteen to ninety-six hours old, indicating that the mucous membrane of young animals is more permeable than in later life.

In addition to the thirty guinea-pigs described in the foregoing tables, twenty others from three to five days old were operated upon and inoculated in the same way. These were permitted to live seven to twenty-four hours and with their lungs forty pigs were inoculated as described. Of the twenty pairs so inoculated twelve pairs showed tuberculous lesions at the end of six weeks, while eight pairs were free.

Summary: Of fifty guinea-pigs experimented upon, in twenty-eight (or 56 per cent) tubercle bacilli reached the lungs within twenty-four hours after inoculation; some in as short a time as four hours; while in twenty-two (or 44 per cent) the results were negative.

The experiments to this point apparently show that tubercle bacilli passed readily and quickly through the intestinal wall, and reached the lungs in a short time through the thoracic duct. However, the results obtained in the ten animals kept as controls throw some doubt on the accuracy of the method followed.

As stated before, sixty-five guinea-pigs were operated upon and inoculated, fifty were permitted to live from four to twenty-four hours, five died from unknown causes, and ten were permitted to live six weeks, when they were chloroformed. The autopsy findings are given in Table No. IV.

Table No. IV.

Autopsies of ten guinea-pigs inoculated directly into the stomach, through an incision in the abdominal wall and permitted to live six weeks.

G.P. No.	1083. No. XI.	1083. No. X.	1083. No. IX.	1078. No. IV.	1078. No. I.	1000. No. I.	1009. No. I.	1002. No. V.	1047. No. VI.	1039. No. I.
Weight	112	125	95	135	110	140	160	210	150	265
Spleen	× ×	× ×	× ×	× ×	× ×	× ×	× ×	× ×	× ×	× ×
Liver	× ×	×	× ×	× ×	× ×	× ×	× ×	× ×	× ×	
Lungs	× ×	......	× ×	× ×	× ×	× ×	× ×	× ×	× ×	× ×
Thoracic gland	×	......	× ×	× ×	× ×	× ×	× ×	× ×	× ×	
Omentum	×	× ×	× ×	× ×	× ×	× ×	× ×	× ×	× ×	× ×
Omentum attached to stomach	×	......	×	×	×	×	×	×	×	
Omentum attached to abdominal wall	×	×	×	×	×	× ×	×	×	×	× ×
Point of incision (laparotomy)	× ×	×?	× ×	× ×	× ×	× ×	×	× ×	× ×	×
Stomach	×	×	×	×	......	×	......	×	......	
Intestine (large)	×	×	×	× ×	× ×	×	......	×	×	
Intestine (small)	× ×	× ×	× ×	× ×	× ×	×	×	×	× ×	
Mesenteric gland	× ×	× ×	× ×	× ×	× ×	×	× ×	× ×	× ×	
Left superficial inguinal gland	× ×	× ×	×	×	×	× ×	×	×	× ×	× ×
Right superficial inguinal gland	......	......	......	......	......	×	×	×		
Left subscapular gland	......	× ×	......	×	×	......	×			
Right subscapular gland	......	......	......	......	......	......	×			

× Signifies tuberculous lesions. The relative extent of the lesions in the organs is indicated by the number of crosses.

The ten autopsies may be summarized as follows: lungs, liver, and spleen show extensive tuberculosis; both the large and small intestines show tuberculous foci, involving the submucous lymph nodes; mesenteric glands greatly enlarged and caseous; stomach involved in six of the ten cases. The omentum was greatly thickened and studded with nodules varying from one to three millimeters and in all ten cases attached to the serous coat of the stomach at or near the point of inoculation. In all, the incision in the abdominal wall had healed with marked induration, the tissue showing on section small yellow caseous foci in which tubercle bacilli were found. To this indurated mass the thickened omentum was strongly attached. In all ten cases the left superficial inguinal gland was enlarged and caseous; in three the right superficial inguinal gland was also involved. The left subscapular gland was enlarged and caseous in four, and the right subscapular in one. The stomach lesions were found upon histological examination to involve chiefly the submucous tissue.

From the distribution of the lesions it appears that infection occurred not only by the passage of tubercle bacilli through the mucous membrane of the intestine, but also directly through the wound in the stomach caused by the hypodermic needle, and it is possible that in spite of the precautions taken tubercle bacilli were deposited on the edge of the wound when the needle was withdrawn. This latter view is supported by the fact that in all cases there was thickened omentum attached to the stomach wall at or near the point of inoculation, an indurated tuberculous mass around the incision made in the abdominal wall, and involvement of the left superficial inguinal gland. It appears that inoculations into the alimentary tract should be made without the production of a fresh wound of this tract in order to obtain results not open to criticism.

CONCLUSION.

In view of the results of our control experiments, we feel unable to draw any positive conclusions from our work since it is possible that infection took place through the blood or lymph channels to some extent, at least. At the same time the distribution of the lesions convinces us that passage of tubercle bacilli through the intestinal wall did take place, and we regard our results, on the whole, as giving confirmatory evidence of the work of others quoted in the body of this paper, demonstrating the importance of the alimentary canal as a portal of infection in tuberculosis.

AGGLUTINATION STUDIES IN TUBERCULOSIS.*

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Our knowledge of the agglutinins is at present somewhat imperfect. There is no definite knowledge of the source from which they are derived and the great diversity of opinion as to the cause of the phenomenon of agglutination renders it highly probable that the true explanation is as yet unknown. The relation that the agglutinating reaction bears to the general subject of immunity has been the subject of much study. Briefly stated it may be said that at present the existence of agglutinins in a serum is not regarded as having any part in the phenomenon of immunity. The agglutinins may be absent in a serum exhibiting a high degree of immunity and present when no such condition exists. It is now believed, however, that the presence of agglutinins affords an index to the degree of immunity present and that as the agglutination test is high or low, or subject to an increase or a decrease we may determine the resistance of the organism to the special bacterium tested for.

While the agglutination test has been applied in a number of diseases the only practical results thus far obtained have been in typhoid fever, Malta fever, and to some extent, in tuberculosis. The study of the agglutinating reaction in tuberculosis has been actively carried on for the past ten years. It was first applied as a means of recognizing early tuberculosis. There is now a mass of evidence, however, against the test of being of any value in this condition. That the agglutination test, as a means of recognizing incipient tuberculosis, was doomed to failure is apparent when the following facts are considered. In the first place if we accept the statistics of Naegeli, and the more recent ones of Burkhardt,[1] as correct it becomes apparent that the

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body cells of most, if not all individuals, have been stimulated to some degree against the tubercle bacillus. This offers a ready explanation of the fact that the serum from the majority of healthy individuals will agglutinate the tubercle bacillus.

In addition to this factor is that of inherited immunity. It is becoming more and more the belief of those working in tuberculosis that tuberculous parents are capable of transmitting a certain degree of protection to their offspring and that the danger to the child is not so much one of heredity as one of infection after birth. It is pointed out that tuberculosis is gradually, if slowly, diminishing in those races which have been longest exposed to its ravages. Furthermore, those races which only comparatively recently have had tuberculosis introduced among them are particularly susceptible, and offer but little resistance to the inroads of the disease. This applies particularly to the negro and American Indian. In these people the death rate from tuberculosis is not only higher than that of the white race (two to four times) but in addition the disease in the majority of cases is of the acute or subacute rather than of the chronic type. Clinically these facts are well known.

The demonstration of an inherited immunity, at least in so far as the agglutination reaction is concerned, fails of proof in the work so far reported. It has already been demonstrated that the serum of new born children lacks many of the agglutinins found later in adult life, and believed in many instances to be normal rather than acquired through previous infection. According to the recent investigations of Salge, an absence of agglutination for the tubercle bacillus was met with in sixty out of eighty children; forty of these children were under three months of age, while of twenty positive tests, eight occurred in children over one year old. Schreiber has shown that very young children show no effects from doses of tuberculin which in adults are capable of producing a marked reaction. Whether this small amount of laboratory evidence can outweigh the mass of clinical evidence is questionable. It is interesting, however, if for no other reason than that it affords additional proof that in the majority of cases infection with the tubercle bacillus occurs in early life, either through the milk as suggested by von Behring, or through infection of the house. In the latter instance children are particularly exposed to infection in crawling about the floor.

Recent work on agglutination in tuberculosis has been devoted to determining its value in estimating the degree of immunity obtained by means of specific or other forms of treatment and in forming a prognosis. A number of workers have shown that under specific treatment with tuberculin or one of the anti-tuberculous sera the agglutination reaction can be greatly increased. This is taken to indicate that the agglutination reaction, if not a part of the immunizing process, at least pursues a parallel course, for in addition a decrease in the agglutination power or a failure to increase is usually attended by an unfavorable outcome.

That even the ordinary hygienic dietetic treatment is capable of increasing the agglutinating power of the blood, although never to the degree obtained by specific treatment, was demonstrated by Ravenel and myself[2] two years ago. Within certain limitations which will be considered later, it now seems apparent from the evidence at hand that a low agglutinating reaction is of unfavorable import. Thus advanced cases, as a general rule, agglutinate low, some claiming that in many of these cases the agglutinating power of the blood is entirely lost. In my own experience, while I can confirm the almost universally low agglutinating reactions in advanced cases, a complete loss of agglutination (at least up to 1–5) has been rarely encountered.

Advanced cases agglutinate low, probably owing to the fact that the natural defences have been greatly weakened. According to Welch,[3] "the struggle between the bacteria and the body cells in infections may be conceived as an immunizing contest in which each participant is stimulated by its opponent to the production of cytotoxins hostile to the other, and thereby endeavors to make itself immune against its antagonist." That the body defences are able to maintain the upper hand for years, even in the presence of extensive pulmonary damage, is a well-known clinical fact. That such individuals are capable of giving a high agglutinating reaction was shown by Ravenel and myself and on observations in the present series.

During the past year I have continued the study of the agglutination reaction as met with in cases of advanced tuberculosis at the Phipps Institute and in cases under treatment at the White Haven Sanatorium, and in addition have used it in negroes in the wards of the Philadelphia Hospital for the purpose of contrasting the resistance offered by members of this race to that met with in the white race.

The test was also applied to effusions of various kinds obtained during life and to fluids obtained from the serous cavities shortly after death.

Advanced cases. — Nineteen advanced cases, in the Phipps Institute, were studied with results similar to those obtained by Ravenel and myself in fifty-nine cases previously reported. The results obtained in these seventy-eight cases were as follows:

11	Agglutinated	1– 5.
40	"	1–10.
24	"	1–15.
1	"	1–20.
1	"	1–25.
1	"	1–30.

The three patients agglutinating above 1–15 were examples of the extremely chronic type of the disease in whom the tendency of the disease is towards the formation of fibrous tissue rather than softening and tissue destruction. Such individuals unquestionably have a higher degree of resistance than those in whom the disease runs an acute or subacute course. While many of them eventually die of tuberculosis, not a few succumb to some intercurrent infection.

Cases treated at the White Haven Sanatorium. — During the past year fifty-four cases at the White Haven Sanatorium were studied. Combined with nineteen previously reported by Ravenel and myself there are available seventy-three cases.

11	Agglutinated	1–10.
32	"	1–15.
17	"	1–20.
12	"	1–25.
1	"	1–30.

Of the fifty-four cases studied during the past year, twenty-six were tested a second time, after they had been under treatment from two to three months. Of six which agglutinated 1–10 on admission, five showed an increase (in two from 1–10 to 1–20; two others from 1–10 to 1–25). Of twelve agglutinating 1–15 on admission, three showed an increase; of six agglutinating 1–20, four remained unchanged, and two showed a decrease; two agglutinating 1–25 remained unchanged. The nineteen cases previously reported were selected from among the most favorable patients in the sanatorium and had been under treatment for from four to twelve months. This group is interesting from the fact that sixteen of the nineteen agglutinated 1–20 or higher, while of the seventy-six advanced cases, sixty-six did not agglutinate above 1–15. In the fifty-four sanatorium cases studied during the past year no effort at selection was made, the cases being taken routinely as they were admitted. Within certain limitations the agglutination reaction in these cases was high in those which were clinically favorable, and correspondingly low in the unfavorable cases. The exceptions were the cases with a history of having had the disease for a long time; two of these advanced cases had an agglutination of 1–20, while two others which were favorable from a clinical standpoint agglutinated only 1–10.

Negroes. — Agglutination tests were made on twenty-six negroes, twenty-one having tuberculosis in various stages and five being healthy able-bodied porters. The following results were obtained:

Advanced cases, 12: 2, no agglutination; 4 agglutinated 1–5, 5 agglutinated 1–10, 1 agglutinated 1–15.
Moderately advanced, 5: All agglutinated 1–10.
Incipient cases, 4: 2 agglutinated 1–15, 2 agglutinated 1–25.
Non-tuberculous, 5: 3 agglutinated 1–10, 2 agglutinated 1–15.

It is at once evident, that, so far as the agglutination test is concerned, these individuals differ in no particular from a similar group of whites. Thus the advanced cases give a low agglutination while the more favorable and incipient cases give a correspondingly high reaction. The five apparently healthy cases all agglutinated.

As has been pointed out the explanation of a high agglutinating reaction in cases with extensive pulmonary involvement, but of long standing, is reasonably satisfactory on the ground of acquired resistance, the result of continued stimulation on the part of the body cells. In conclusion three of the paper by Ravenel and myself we stated that a low agglutination was of unfavorable prognostic significance.

Further studies have convinced me that this is not always true and more especially so if but one observation is made. As has been already noted five out of six cases giving an initial agglutination of 1–10 later, as the result of treatment, had their agglutination reaction distinctly increased.

There are a number of cases, however, in which even with a persistently low agglutination good clinical results are obtained. In such individuals it seems reasonable to assume that while they have a low degree of immunity the particular strain of tubercle bacillus with which they have become infected is of low virulence. Welch's hypothesis already referred to compares the struggle between the invading bacteria and the body cells to an immunizing contest in which each struggles for supremacy. On this hypothesis low resistance on the part of the body cells and high virulence of the invading bacilli mean disease of an acute type. The virulence of the invading bacteria being low the necessity for a strong resistance on the part of the body cells becomes correspondingly less. Post-mortem evidence of tuberculosis which during life has never given any manifestations of its existence, is probably an example of great resistance on the part of the body cells combined with infection by bacilli of varying degrees of virulence.

Fluid obtained at autopsy. — A study of the fluids obtained from the pericardial, pleural, and peritoneal cavities and of fluid obtained from the cerebrospinal canal gave some interesting results. These fluids were obtained both from tuberculous and non-tuberculous subjects. In addition to determining the agglutinating reaction, the percentage of albumen was estimated and in many of them the cellular constituents were determined.

The pericardium. —

> 1 did not agglutinate, 10 agglutinated 1–5, 17 agglutinated 1–10, 6 agglutinated 1–15, 1 agglutinated 1–20, 1 agglutinated 1–25.

Six non-tuberculous cases gave the following results:

> 1 did not agglutinate, 1 agglutinated 1–5, 4 agglutinated 1–10.

The albumen estimations ranged from one per cent, the lowest, to four per cent, the highest, in the tuberculous cases, and from one and one-quarter to six per cent in the non-tuberculous cases.

Of nineteen tuberculous cases in which the character of the cells was determined, three showed small lymphocytes alone; nine small and large lymphocytes, and seven polymorphonuclear or endothelial cells in association with small and large lymphocytes.

Four of the non-tuberculous cases showed the presence of small and large lymphocytes, polymorphonuclear, and endothelial cells, the lymphocytes, however, being few in number. In one case polymorphonuclear cells alone were found.

The pleura. — Twelve pleural fluids were obtained from tuberculous cases.

1 did not agglutinate, 1 agglutinated 1–5, 8 agglutinated 1–10, 2 agglutinated 1–15.

The albumen estimations ranged from one and three-quarters to five per cent. In ten of these twelve cases, the small lymphocyte was the predominating cell and in one was the only form of leucocyte present.

The fluid from four non-tuberculous cases agglutinated as follows:

1 did not agglutinate, 1 agglutinated 1–10, 1 agglutinated 1–15, 1 agglutinated 1–20.

The albumen percentage ranged from one and one-half per cent to four per cent. Two showed the predominating leucocyte to be the polymorphonuclear, one contained numerous endothelial cells and a few small lymphocytes and another contained nothing but lymphocytes both large and small.

The peritoneum. — Of twenty-five tuberculous cases:

2 did not agglutinate, 12 agglutinated 1–5, 7 agglutinated 1–10, 3 agglutinated 1–15, 1 agglutinated 1–20.

The albumen estimations ranged from one-half to three and one-half per cent. The albumen estimations in these fluids was much lower than either the pericardial or pleural fluids. It will also be noted that the average agglutinations in these fluids is lower than in either of the others.

In nineteen of these fluids, six showed the small lymphocytes alone and nine the small or large lymphocytes in association with polymorphonuclear or endothelial cells. In one case each the small lymphocyte, the polymorphonuclear and the endothelial cells were the only cells present. Two of the fluids showed an excessive amount of fibrin.

Three non-tuberculous fluids showed:

1 did not agglutinate, 1 agglutinated 1–5, 1 agglutinated 1–10.

The albumen ranged from one to two and one-half per cent. The cellular elements, as in both the non-tuberculous pericardial and pleural fluids, were of all varieties.

At this point it should be stated that in no instance was the agglutination reaction identical for the two or three fluids obtained from a single case, thus while the pericardial fluid would agglutinate one to ten the others would agglutinate higher or lower.

Cerebrospinal fluid. — In direct contrast to the agglutination results mentioned above were those obtained with cerebrospinal fluid. Twelve of these fluids were studied. Four were obtained from tuberculous cases, three at autopsy and one during life by lumbar puncture. Eight specimens were obtained by means of lumbar puncture from non-tuberculous children. Ten of these twelve fluids failed to agglutinate the tubercle bacillus and in two others the reaction was doubtful at one to five. In eleven the albumen amounted to but a trace; in one, obtained from a case of non-tuberculous meningitis, there was .75 per cent albumen.

The four fluids from tuberculous cases showed the small lymphocyte to be the predominating cell; in the non-tuberculous cases the polymorphonuclear or endothelial cells predominated.

The fact that the cerebrospinal fluid lacked agglutinating properties and at the same time showed but very slight amounts of albumen suggested the possibility of the albumen content of the fluids having some influence on the reaction. While this may be true the quantity of albumen above a certain amount does not seem to bear any relation to the degree of agglutination. A fluid with five per cent albumen instead of consistently agglutinating higher is just as apt to agglutinate lower than one with but one per cent. So far as the physical appearances of the fluids are concerned there is a distinct difference between those obtained from the cerebrospinal canal and those obtained from the serous cavities. The former are slightly cloudy at the time of puncture but become clear on standing; are usually lacking in sediment and can scarcely be distinguished from distilled water, while the latter are amber or straw colored, with at times a faint greenish tinge. Courmount (translated by M. P. Ravenel, Jour. Amer. Med. Assn., May 19, 1906) has recently published his results obtained with the agglutinating reaction in pleural effusions. He states that the reaction as obtained with pleural effusions is important from the standpoint of prognosis. In a study of one hundred and fifteen cases, many of them traced for a number of years, he found that the mortality was decidedly less in those which agglutinated as compared with those which did not agglutinate; that the proportion of recoveries was high as the agglutinating reaction was high, and that the agglutinating reaction increased or diminished accordingly as the patient tended to recovery or the reverse. This is in accord with the results obtained from the blood serum.

As already stated, the frequency with which tuberculosis is found at autopsy renders it highly probable that the serum from the great majority of individuals has the power of agglutinating the tubercle bacillus. The height of the agglutination gives the index in most cases to the degree of immunity in the individual case.

The studies made of the fluids obtained from the serous cavities of individuals dead from tuberculosis show that they all, with a few exceptions, agglutinated the tubercle bacillus. In other words, the various body fluids, whether normal, in so far as the quantity and the gross appearance is concerned, or pathological, have the power to agglutinate the tubercle bacillus, although the degree of agglutination may be different for each one of the fluids tested from the individual case. Courmont also found that the agglutination reaction as obtained from the serum and the pleural effusion of the same case was not the same. I am unable to add much evidence in regard to the prognostic significance of the agglutinating reaction as found in pleural effusions for the reason that the number of cases studied is too small. The test was applied in nine cases, seven tuberculous and two non-tuberculous, the latter being instances of hydrothorax resulting from chronic heart disease. In two tuberculous cases agglutinating one to twenty, an excellent recovery was made. This was also true of one agglutinating but one to five; the others have not been traced.

The details of the results obtained in nineteen effusions from the pleural and peritoneal cavities and from the knee joint are as follows:

> Pleural: 1 agglutinated 1–5, 4 agglutinated 1–10, 2 agglutinated 1–15, 2 agglutinated 1–20.

The albumen content ranged from seven and one-half to one per cent. The two non-tuberculous effusions contained one per cent albumen each.

> Peritoneal: 1 agglutinated 1–5, 4 agglutinated 1–10, 3 agglutinated 1–15.

One of these effusions was due to peritoneal tuberculosis, three to chronic heart disease, two to cirrhosis of liver, and in two the cause was unknown. The specific gravity ranged from one thousand twelve to one thousand eighteen; the albumen from four per cent to two-tenths of one per cent. In every one of these fluids, seven of which were non-tuberculous, the small lymphocyte was the predominating cell. The cellular content was, as a rule, very small.

Knee joint. — Both effusions agglutinated, one, one to ten, the other, one to fifteen. One was a tuberculous joint, the cause of the effusion in the other case was unknown.

The interesting point in regard to these effusions in contradistinction to Courmont's results is that they all agglutinated the tubercle bacillus whether coming from a tuberculous individual or one suffering from some other pathological condition.

Further studies along these lines may throw additional light on the complex question of immunity in tuberculosis. In so far as the agglutination is concerned our knowledge may be summarized as follows:

1. That the reaction is valueless as a diagnostic agent.

2. That it forms an available means of estimating the degree of immunity attained in tuberculosis by means of tuberculin and other forms of treatment.

3. That the absence of the agglutinating reaction in fluids containing but little albumen, such as cerebrospinal

fluid, renders it highly probable that the agglutinins are closely allied to the albumens.

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REFERENCES.

1. Zeitschrift f. Hygiene, 1906, liii, 139.
2. Medical News, 1906, 1070.
3. Medical News, lxxxi, 721.

FACTORS DETERMINING THE COAGULATION OF BLOOD SERUM BY BACTERIA.*

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The use of culture media composed of a solution of a carbohydrate in a mixture of water and blood serum, colored with litmus, has served to differentiate the various members of a group of closely related bacteria from each other. The most important reactions induced by bacteria in these media are the production of acids from the carbohydrates and the coagulation of the serum.

The study of the factors determining the coagulation of the serum in these media leads us into the domain of physical chemistry. The laws governing the physico-chemical states of colloids are now receiving attention from many investigators, and new facts are being brought to light.

The colloids in blood serum are in a state of solution in the body, and on removal from the body they are changed by several different factors from the state in which they are known as sols to a solid state, when they occur as dry, swollen, coagulated, or precipitated masses and are known as gels.

Pauli[1] states that the only difference between sols and gels is in the greater size of the particles of the latter. The particles of the sols are always so small that through their friction upon each other they are kept in suspension. In this state they appear to be no longer affected by the force of gravity.

The colloids are not dissociated into electro-positive and electro-negative ions as is the case with the crystalloids. The electric charge of a particular colloid appears to be dependent upon the presence in the solution of either electro-positive or electro-negative electrolytes, and hence they move

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toward either the positive or the negative electrode, according to the nature of the electrolytes in the solution.

Pauli[2] found that the addition of neutral salts of the alkalis or the alkaline earths does not impart an electrical charge to the uncharged colloids. Traces of acid, however, impart a positive charge through their positively charged hydrogen ions, while alkalis impart a negative charge through their hydroxyl ions. Salts with an alkaline reaction toward litmus, such as carbonates and the secondary and tertiary phosphates of the alkali metals, render colloids electronegative, while acid salts give a positive charge. This charge is independent of the end-reaction of the solution, as the addition of sodium bicarbonate in appropriate amounts causes it to react faintly acid with phenolphthalein, neutral with litmus, though it has a strongly negative charge.

Iscovesco[3] and his co-workers have reached the conclusion that the peritoneal fluid of the horse contains only electro-positive colloids, while the pericardial fluid contains both electro-positive and electro-negative colloids; that the blood plasma contains electro-positive and electro-negative albumins and globulins, while the serum contains only electro-positive globulins and electro-positive and electro-negative albumins; that the amniotic fluid contains electro-positive and electro-negative albumins and only electro-negative globulins. These facts indicate that albumins and globulins of different electric charge exist side by side in the same fluid, and that these differences are due to chemical union between the colloids and the crystalloids. As long as these combinations remain the same the physical state of the colloids remains unaltered, but slight alterations may lead to marked disturbances.

The colloids appear to be precipitable only through electrolytes and not through non-electrolytes such as urea and sugar. Billitzer[4] has found that if oppositely charged ions are added to a colloid the colloidal particles collect about these ions through electrostatic attraction. In this way aggregates are formed of sufficient size to be brought under the influence of the force of gravity, and they fall to the bottom.

Pauli[5] experimented upon neutral (salt-free) protein and found that the positive metallic ions of the salts of the alkalis were the bearers of the precipitating power, in the order of Li, Na, K, and NH_4, and that the negative ions of the salts exerted an inhibiting effect upon the precipitating power in the following order: Sulphate, acetate, chloride nitrate, bromide, iodide, and sulphocyanate. He found that by rendering the protein electro-positive in its charge through the addition of an acid the effects of salts of the alkalis were completely reversed. The negative ions of the salts acquired a precipitating power extending from sulphocyanate to sulphate, while the metallic ions acquired an inhibiting effect in the order of NH_4 to Li. He found also that the same reversal in ionic effects as is brought about through acids can also be brought about through the addition of the salts of the alkaline earths, Ca, Ba, Sr, to the neutral (salt-free) protein. The salts of the alkaline earths act only indirectly in the reversal of the ionic effects through their action on the salts in the blood serum. This is indicated by the results obtained in acting upon a solution of sodium bicarbonate or disodium phosphate by means of calcium chloride. These two salts have an alkaline reaction because of the OH ions dissociated when they combine with water and split hydrolytically into sodium hydroxide and carbonic or phosphoric acid. Since, however, sodium hydroxide is a stronger base than carbonic acid and phosphoric acid are acids, more OH ions exist in solution than H ions. In the chemical reaction of the alkaline earths and blood serum the calcium hydroxide is much weaker than sodium hydroxide; hence the carbonates and phosphates of the serum bring about an acid reaction.

The carbohydrate-splitting enzymes of bacteria bring about an alteration in the reaction of the serum-water media containing carbohydrates through the formation of organic acids. By this means the colloids in the media are altered in their electric charge and may be brought under the precipitating influence of either the positive H ions of the organic acids resulting from the fermentation of the carbohydrates, or the negative ions of the salts formed by the acids with the alkalis or alkaline earths in the blood serum.

The changes which the colloids may undergo are classified as follows[6]:

A. Changes in temperature lead to setting —
  1. By lowering the temperature.
  2. By raising the temperature.

B. Mechanical shaking produces "conglutination."

C. Physical factors induce "coagulation" —
  1. By alterations in the electric tension between the colloid and its solvent.
  2. By dehydration (or "salting out").

D. Chemico-physical factors cause "precipitation," owing to —
  1. A withdrawal of the H or OH radical of the colloid.
  2. A removal of salts.
  3. The formation of insoluble or irreversible salts.
  4. Heat action.

E. Chemical action accompanied by physical change, owing to the formation of additive compounds between colloids and non-electrolytes by the process of oxidation and reduction.

From the foregoing outline of the changes which colloids may undergo it is probable that the so-called coagulation of the serum in these media is due to either a coagulation induced through an alteration in the electrical tension between the colloids and the solvent, or a precipitation induced by a withdrawal of the hydrogen or hydroxyl radical of the colloid or to the removal of salts.

If we are dealing with a coagulation of the serum this alteration would appear to be due to change in electrical tension of the colloid brought about through the action of the organic acids formed as the result of the action of the carbohydrate fermenting enzymes produced by the bacteria.

If the alteration of the serum in these media falls in the class designated by Mann by the term precipitation, it may be induced by the abstraction of the hydrogen radicals of the colloids by the organic acids, or the removal of salts from the colloid complex to form new compounds with the organic acids.

Caseinogen is a nucleoalbumin combined with calcium. It is at once precipitated upon the addition of an acid, and at the same time the calcium becomes separated from it. In the coagulation of caseinogen by rennet the calcium unites with the caseinogen to form caseins. The coagulation of the serum-water media through the action of bacteria has many similarities to the precipitation of caseinogen.

Caseinogen, which has been freed from calcium phosphate by dialysis, is not coagulated by the rennet ferment. Similarly caseinogen obtained by precipitation with dilute acetic acid is not coagulated by rennet, but on the addition of lime water and careful neutralization with dilute phosphoric acid coagulation with rennet occurs. Hammarsten[7] explains these results by saying that the enzyme induces the conversion of caseinogen into casein and that the calcium phosphate makes the latter separate out in the form of curd. Green[8] believes the curd to be not pure casein but a compound of casein and the calcium salt.

Cole[9] reached the conclusion that the activity of an enzyme is stimulated by anions and depressed by cations, the effect of the ions being determined by their actinizing power. His results have been confirmed and extended by McGuigan, who concluded that the inhibitory power of any salt is inversely proportional to the sum of the solution tensions of its ions, a result which is identical with that arrived at by Mathews for the action of ions on nerve.

The foregoing results and conclusions indicate that the rapidity and extent to which a particular organism is able to bring about coagulation of the serum-water media may be dependent upon two important factors: *a*, alterations in the charge of the colloids; and *b*, the influence exerted upon the enzymes produced by the bacteria by the interaction of the stimulating effects of the anions and the depressing effects of the cations present in the solution. Irregularities in the results obtained at different times are most probably traceable to the second series of factors.

In order to ascertain the factors concerned in the coagulation of blood serum in the Hiss carbohydrate media, two principal lines of experimentation were pursued. The first consisted in ascertaining the influence on the rate of coagulation of the blood serum of such substances as calcium carbonate (marble) and zinc oxide when placed in the culture media. The second method consisted in studying the influence of old, acid culture filtrates on the rate of coagulation when added to the media along with different substances which neutralized the acid in the filtrate.

The influence of calcium carbonate in inhibiting the coagulation of blood serum by some organisms is relatively slight, so that it is necessary to conduct the experiment at room temperature in order to note the inhibitive influence as shown by the absence of coagulation or its later appearance than in control cultures. At body temperature the inhibitive power of calcium carbonate is so slight for some bacteria as to escape detection.

Even with evident inhibition of the coagulation of the blood serum by calcium carbonate it is difficult to exclude all other factors and attribute the effect to the neutralization of the acid formed from the carbohydrate. With neutralization of the acid the coagulation may result through the influence of at least two other factors, viz.: the alteration of the electric charge of the proteids of the media through the chemical changes induced, and the simultaneous production of a coagulating enzyme.

Table I.

Carbohydrate.	24 hours.		48 hours.		72 hours.		144 hours.		10 days.	
	Plain.	Marble.	Plain.	Marble.	Plain.	Marble.	Plain.	Marble.	Plain.	Marble.
Streptococcus lacticus.										
Dextrose	b	a	b	b	b	b	b	b	b	b
Lactose	a	a	b	b	b	b	d	d	d	d
Saccharose	a	a	b	a	b	b	d	b	d	b
Levulose	a	a	b	b	b	b	d	d	d	d
Inulin	a	a	b	b	b	b	d	d	d	d
Maltose	a	a	b	b	b	b	b	b	b	b
Milk	a	a	b	b	b	b	b	b	b	b
Micrococcus aureus.										
Dextrose	b	b	b	b	b	b	b	b	c	b
Lactose	b	b	b	b	b	b	b	b	b	b
Saccharose	a	a	b	a	b	b	b	b	c	b
Levulose	b	a	b	b	b	b	b	b	d	b
Inulin	a	a	a	a	b	b	b	b	b	b
Maltose	b	b	b	b	b	b	b	b	b	b
Micrococcus albus.										
Dextrose	b	a	b	a	b	b	b	b	d	b
Saccharose	a	a	a	a	a	a	b	b	d	b
Levulose	a	a	a	a	a	a	b	a	d	b
Inulin	a	a	a	a	b	a	b	a	b	a
Maltose	b	b	b	b	b	b	b	b	c	b

Legend.

a: unchanged. b: slightly acid. c: distinctly acid. d: acid and coagulated.

Table I. shows the inhibiting influence of calcium carbonate upon the relative degree of acidity induced and the rate of coagulation. It will be seen that for some organisms, with most of the carbohydrates employed, there is very little difference in the results obtained. For other organisms, however, the difference is sufficiently marked to leave no doubt that the effect of the fermentative activity of the organism is altered.

In some instances the inhibition manifests itself in a lower degree of acidity induced, while in others the production of acid is entirely inhibited. In other instances there is both a lower degree of acidity and an entire absence, or abeyance, of coagulation of the serum.

The question arises as to whether the retardation in the effects of the organisms under the influence of calcium carbonate is due to an inhibition of growth or whether it is due to the neutralization of the acids formed. In order to ascertain whether there is an inhibition of growth, plate cultures were made and the relative number of bacteria determined in the treated and untreated cultures (see Table II.).

TABLE II.

Development of colonies on plate cultures.

Culture.	Dextrose.		Lactose.		Saccharose.		Milk.	
	Plain.	Calcium Carbonate.	Plain.	Calcium Carbonate.	Plain.	Calcium Carbonate.	Plain.	Calcium Carbonate.
Streptococcus lacticus.	—	+ +					+ + +	+ + +
Micrococcus aureus ..	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +		
Micrococcus albus...	+	+ +			—	+ + +	+ + +	+ + +

— = No growth.
+ = Slight growth.
+ + = Numerous colonies.
+ + + = Colonies very numerous.

The plate cultures demonstrated that the treated cultures contained more bacteria, in some instances, than the untreated cultures. In fact, some of the untreated cultures were found to be sterile. This result is, no doubt, to be attributed to the germicidal influence of the organic acids formed by the bacteria. The plate cultures give no indication that the diminished effects noted in the cultures, induced by the calcium carbonate, were due to inhibition of the growth of the bacteria. Since the principal difference noted between the two sets of cultures was production of a lower degree of acidity, it is probable that this was also the cause of the retardation of the coagulation of the serum.

The use of zinc oxide for the purpose of neutralizing the acid formed by the bacteria from the carbohydrates gave results of the same general character as those obtained when calcium carbonate was used (see Table III.). In these experiments it is evident that a part of the inhibitive influence noted is due to the greater alkalinity of the media or to direct germicidal action of the zinc oxide, and hence to direct inhibition of growth rather than to inhibition of the action of the acid formed from the carbohydrate.

Plate cultures made from treated and untreated cultures showed that the effect obtained with some bacteria was due to the inhibition of growth through the germicidal action of the zinc, as the treated cultures, which had undergone no alteration, were found to be sterile, while the control cultures contained large numbers of bacteria (see Table IV.).

TABLE III.

Streptococcus lacticus.

Carbohydrate.	24 hours.		48 hours.		72 hours.		144 hours.		10 days.	
	Plain.	Zinc Oxide.	Plain.	Zinc Oxide.	Plain.	Zinc Oxide.	Plain.	Zinc Oxide.	Plain.	Zinc Oxide.
Dextrose	a	a	b	b	b	b	b	b	b	b
Lactose	d	a	d	a	d	a	d	b	d	b
Saccharose	d	a	d	a	d	a	d	a	d	a
Inulin	d	a	d	a	d	a	d	a	d	a
Milk	b	a	b	a	b	a	d	a	d	a

Micrococcus aureus.

Carbohydrate.	24 hours.		48 hours.		72 hours.		144 hours.		10 days.	
	Plain.	Zinc Oxide.	Plain.	Zinc Oxide.	Plain.	Zinc Oxide.	Plain.	Zinc Oxide.	Plain.	Zinc Oxide.
Dextrose	b	b	d	d	d	d	d	d	d	d
Saccharose	d	a	d	a	d	a	d	a	d	a
Inulin	b	a	b	a	b	a	b	a	b	a
Milk	b	a	b	a	b	a	d	a	d	a

Legend.

a: unchanged. b: slightly acid. c: distinctly acid. d: acid and coagulated.

TABLE IV.

Development of colonies on plate cultures.

Culture.	Dextrose.		Maltose.		Inulin.		Milk.	
	Plain.	Zinc Oxide.	Plain.	Zinc Oxide.	Plain.	Zinc Oxide.	Plain.	Zinc Oxide.
Streptococcus lacticus.	++	—	+	—			+++	—
Micrococcus aureus					+++	—		
Bact. acidi lactici					+++	—		

— = No growth.
+ = Slight growth.
++ = Numerous colonies.
+++ = Colonies very numerous.

Zinc oxide appears to possess a more marked germicidal action for some bacteria than for others, as it was without any influence upon the degree of acidity induced or the rate of coagulation in some of the cultures employed in these tests.

The second series of experiments appears to throw more light upon the factors concerned in the coagulation of blood serum than was afforded by those of the first series.

A series of cultures capable of breaking up carbohydrates with the formation of acid was cultivated about a month at 37.5° C. in bouillon containing dextrose and levulose. These cultures were then filtered through a sterile Berkefeld filter, and the filtrate employed for various tests on the Hiss media.

In its unaltered state this filtrate showed an acidity of five per cent, and when added in equal amounts to two cubic centimeters of the Hiss medium produced a solid coagulum almost immediately. Much smaller amounts of the filtrate produced a decided acid reaction in the two cubic centimeters of the medium.

The next point to be determined was whether the coagulation of the medium took place if the acidity of the filtrate was first neutralized by different reagents. These tests indicated that no coagulation was induced by the filtrate after neutralization with such reagents as potassium or ammonium hydroxide, or sodium carbonate.

According to Fischer and Ostwald[10] both organic and inorganic acids are capable of precipitating electro-negative colloids, while alkalis precipitate electro-positive colloids; and generally no amount of acid will precipitate an electro-positive colloid, and no amount of alkali will precipitate an electro-negative one.

In the light of the discoveries of Iscovesco[11] and his co-workers, the organic acids formed in the Hiss serum-water media would be capable of acting only on the electro-negative albumins, if the coagulation of the serum is due merely to the acids formed. Since the globulins of the serum are, however, precipitated by acids, it is probable that the results obtained by Iscovesco are due to the electrolytes present in the fluids examined, and not to the native properties of these substances.

Pauli[12] concludes that native protein carries a negative charge which is derived from the hydroxyl ions that are split off from the salts of the serum, that is, the carbonates and phosphates.

The possibility that the coagulation of the blood serum may be due primarily to the formation of a coagulating enzyme by the bacteria was next taken into consideration. Rennet coagulates caseinogen somewhat slowly as compared with the precipitating effect of acids, which occurs almost instantly. Likewise the precipitation of blood serum by the acid filtrates occurs quickly, but on standing it assumes a character which indicates that a coagulating enzyme is also acting, since the serum assumes a firm consistency after several hours.

The presence of a coagulating enzyme in these culture filtrates has been assumed for a long time, but thus far the direct evidence of its presence is lacking. These filtrates contain a coagulating enzyme as shown by the separation of the enzyme by the method employed by Conn,[13] and these enzymes behave just the same as rennet. Rennet enzyme is most active in acid solution, and in this respect the culture filtrates show identical characteristics.

While it is evident that the organic acids are of primary importance in the coagulation of blood serum, the experiments indicate that the alteration of the colloids is due to the combined action of the acids and a coagulating enzyme.

The results obtained appear to support the following conclusions:

1. The coagulation of the Hiss serum-water media by bacteria is inhibited by calcium carbonate.
2. The inhibition of the coagulation is due to the neutralization of the organic acids formed from the carbohydrates in the media.
3. Zinc oxide exerts the same influence upon the effects produced by some bacteria, while for others it is germicidal.
4. The acid filtrates of old cultures produce almost instantaneous precipitation of the media, conforming in this respect to the effects produced by dilute acids.

5. Boiling the acid filtrates does not inhibit their precipitating powers, but does inhibit the coagulating powers, while neutralization of the acid entirely inhibits this action, indicating that coagulation is due to the presence of the organic acids and a coagulating enzyme produced by the bacteria.

6. The exact manner in which the coagulation of the serum is induced is not determined. It seems evident that the organic acids, formed as the result of the fermentation of the carbohydrates, change the electric charge of the colloids in the media. Whether, in addition to this, the coagulating enzymes bring about a chemical union with the calcium salts and the colloids, as in the coagulation of caseinogen, cannot be stated. It appears quite probable, however, that the processes and effects are of a similar nature to the coagulation of caseinogen by rennet.

7. These studies indicate the probable relation of bacteria and their metabolic products to certain pathological changes seen in disease, especially to the necroses. These changes are most probably due to the combined action of the enzymes and metabolic products of the bacteria upon the cells and fluids of the body.

BIBLIOGRAPHY.

1. Pauli, Wolfgang. Physical chemistry in the service of medicine. New York, 1907, 139.
2. Pauli. Ibid., 143.
3. Iscovesco. Compt. Rend. Soc. Biol., 1906, lxi, 195, 355, 378, 470, 568.
4. Billitzer. Ann. d. Physik, 1903, quoted by Pauli, 141.
5. Pauli. Ibid., 148.
6. Mann, Gustav. Chemistry of the proteids. London, 1906, 272.
7. Hammarsten. A Text-book of Physiological Chemistry. New York, 1900, 389.
8. Green. Ibid., 240.
9. Cole. Hill's Recent Advances in Physiology and Biochemistry. London, 1905.
10. Pauli. Ibid., 146.
11. Iscovesco. Loc. cit.
12. Pauli. Ibid., 146.
13. Conn. Centralblatt f. Bacteriologie, xvi, 914.

THE INFLUENCE OF BLOOD SERUM UPON AUTOLYSIS.*

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In the course of some other experiments small pieces of the tumors excised at operation from a case of Hodgkin's disease were kept at 37° C. in human blood serum, sealed in test-tubes, for several months. At the end of three months it was a great surprise to find that the bits of tissue, to the naked eye, had not changed greatly in appearance. When sections were made, however, and stained in hematoxylin and eosin, it was found that only a few scattered nuclei stained. The architecture of the tissue was well preserved, but the cells, nuclei, and interstitial tissue all stained diffusely in eosin. Following this observation a series of experiments was undertaken to determine what influence, if any, blood serum has upon autolysis.

Experiments dealing with this particular subject have not given, so far, very definite results. Baer and Loeb[1] in 1905 showed by chemical methods that blood serum of the dog inhibits autolysis of dog's liver. This property is not injured when the serum is heated to 56° C., and undergoes but slight change after heating diluted serum at 100° C. This property resides not in the globulin portion of the serum, which indeed hastens autolysis, but in the albumen fraction. Baer and Loeb concluded that this property of blood serum was neither dependent upon the alkalinity of the serum nor upon an anteferment action, but was due to some unknown substance of the serum. Wiener,[2] later, repeated Baer and Loeb's work and confirmed their findings. But he showed that small quantities of acid increased autolysis while the addition of alkalis to the control salt solution inhibited autolysis. He criticised Baer and Loeb's conclusions and suggested that the power of the serum to inhibit autolysis was due to its alkaline reaction. He found, however, that an

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alkaline reaction equal to that of the blood was not sufficient to inhibit autolysis in his control experiments carried out with salt solution.

Schryver[3] has noted that autolysis of the liver is greatly inhibited by blood serum. Launoy[4] found that if rabbits' livers were kept in rabbit serum the histological structure was well preserved and the nuclei stained for at least thirty-eight hours, while if tissue was kept in salt solution the nuclei of the cells of the liver soon lost their power to stain. Wells,[5] too, has studied this question histologically. In his work upon the relation of autolysis to the histological changes occurring in necrotic areas, he described an experiment which showed that dog's serum is capable of inhibiting autolysis of the same dog's liver to a marked degree. This property was injured by heating the serum to 80° C. for thirty minutes. He concludes that in infarcts the intracellular proteolytic enzyme seems to attack the proteid structures of the cells but little. This depends upon the presence in the plasma of antibodies or of some heat susceptible substances which check the action of the autolytic enzymes. He also suggests that the alkalinity of the plasma exerts a retarding influence upon autolysis of the tissue.

It has been known for some time, through the work of Hann,[6] Landsteiner,[7] Glaessner,[8] Cathcart,[9] Oppenheimer and Aaron,[10] and Levene and Stookey,[11] that trypsin will not digest unheated blood serum. Levene and Stookey have obtained much the same result with unheated egg albumen. Both Landsteiner and Cathcart have shown that this antitryptic action resides in the albumen fraction of the serum, and Cathcart noted that this action was destroyed by heating the serum to 70° C. Recently Opie[12] has described a property of blood serum which inhibits the action of the proteolytic ferments of leucocytes. This anti-leucoproteolytic action is only specific to a certain degree; it resides in the albumen fraction of the serum and is destroyed by a temperature of 80° C.

The following experiments were carried out upon the livers, and in a few instances upon the kidneys of normal dogs.* The dogs were etherized and bled to death by cutting the carotid and femoral arteries or the abdominal aorta. This blood was collected aseptically and the serum which separated out was used for the experiments. Portions of the liver and the kidneys were then removed aseptically, cut into small pieces (one-half to one centimeter square), and placed in small flasks with ten to twenty centimeters of .85 per cent salt solution blood serum, or any fluid which it was desired to use. After the addition of two to three cubic centimeters of toluol, the flasks were shaken thoroughly, stoppered with rubber caps, and kept at 36.5° C. At intervals, one of the pieces of tissue was removed from the flask, fixed in Zenker's solution, and later studied histologically. The progress of the change taking place in the bits of liver and kidney were thus studied roughly by the general consistency and naked eye appearance, and more accurately by the histological structure. At first, as a control against bacterial growth, cultures were made from the pieces of tissue when they were removed from the flask. This was soon found to be unnecessary, for in only one or two instances was there a bacterial contamination, and this was readily discovered in stained sections.

In the first series of experiments pieces of liver and kidney were kept in undiluted dog's serum and for control in .85 per cent salt solution. When the flasks are kept at 36.5° C. very marked differences are readily noted after twelve to twenty-four hours between the tissues which are in salt and those which are in serum. In salt solution, after twelve to twenty-four hours, the pieces of liver begin to soften, and a sediment forms in the bottom of the flask. The softening increases rapidly, becoming marked at the end of forty-eight to sixty hours. After ten days to three weeks the pieces of tissue are soft, friable, shrunken, and the bottom of the flask is covered with a granular sediment. Histologically the nuclei refuse the hematoxylin stain completely after twelve to eighteen hours. The cells look opaque, granular, and are slightly shrunken, some of them are filled with fine refractile granules. After twenty-four hours gradual dissolution of the protoplasm of the cells takes place. The cells shrink, the outlines become indefinite, the protoplasm becomes coarsely granular, vacuolated, and finally may appear as an indefinite reticulated mass.

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* I should like to express my thanks to Dr. J. Edwin Swet, of the University of Pennsylvania, who very kindly furnished me with the material for this investigation.

The changes in the kidney were the same as those in the liver, though they progressed more slowly. The epithelium of the convoluted tubules and the ascending loops of Henle were affected first, next the collecting tubules, and descending loops of Henle, and finally the glomeruli, the nuclei of the cells of which occasionally stained even after several days.

In blood serum the changes in the liver were entirely different. Macroscopically the livers remained quite firm and the serum showed at first only a slight turbidity. Sometimes a slight sediment developed after three to four weeks. At the end of fifteen to twenty hours the pieces of liver looked rather white and were moderately firm. If they were cut in two it was readily made out that only the extreme edge of the tissue was firm. About the margin there was a firm whitish zone scarcely a millimeter in thickness, while the center of the tissue was moderately soft. After forty-four to sixty-three hours the firm peripheral zone became wider, and by eight days to two weeks the entire bit of tissue was quite firm and very pale. Occasionally the tissue had a waxy appearance. Pieces of liver removed from the serum after twenty-six to thirty days were still quite firm. In two experiments the livers were kept in serum for two and three months. At the end of this time the bits of tissue were rubbery, much more pliable than at the end of three weeks.

Microscopically the difference between the salt and serum livers was very marked. In serum the nuclei of the liver cells were visible and stained well after forty-three to sixty-eight hours. In one instance a few nuclei could still be seen after eight days. The nuclei were only preserved, however, about the margin of the section. The center of the section looked much like the livers kept in salt solution. This narrow band of well preserved cells corresponded to the firm marginal line seen macroscopically. It could be noted in all the sections that a layer of two or three cells forming the outermost edge of the section never contained staining nuclei. The protoplasm of the cells in the stained zone was slightly granular, and as the nuclei disappeared, minute refractile granules formed. These are evidently the myelin bodies described by Albrecht. The outline of the cells was well marked. After sixty-eight hours the microscopical differences between the salt and serum livers were not so definite, though the cells of the serum livers were much more distinct in their outlines, and did not show nearly so much dissolution as did the cells of the livers kept in salt solution. The following protocol will serve as a type of the findings in this experiment which was repeated many times:

XIII. Feb. 3, 1907. — Normal bitch, etherized, bled from aorta, liver removed 11.30 A.M. Liver used 2 P.M. Serum from same dog. Four pieces of liver put in .85 per cent salt solution, four pieces put in serum.

TABLE I.

		20 Hours.	44 Hours.	8 Days.
85% NaCl.	Macroscopic	Quite soft.	Very soft.	Very soft.
	Microscopic	No nuclei; fair preservation of cells.	No nuclei; cells shrunken with poor definition.	Granulation, shrinkage and fusion of cells.
Serum.	Macroscopic......	Firm zone on outer edges; soft in center.	Firm and white.	Very firm.
	Microscopic......	Many nuclei about margin; cell protoplasm excellently preserved.	Many nuclei about margins; cells well preserved, containing refractile granules.	No nuclei; no shrinkage or fusion of cells; few refractile granules in marginal cells.

The fact that only the extreme periphery of the piece of tissue is preserved well in serum is due to the fact that the serum penetrates very slowly into the liver tissue.

This was well demonstrated in another set of observations. For a certain number of experiments human liver was used from autopsy material, which was obtained from three to eighteen hours after death. In five instances it was found that the nuclei of the human liver, which were allowed to undergo autolysis in salt solution, stained, and the protoplasm of the cells remained intact for much longer periods than when the livers of bled dogs were employed. In two cases the nuclei had disappeared by forty-eight hours; in two instances they stained faintly after ten days, and in one instance they were definitely visible after twenty-seven days. In serum the preservation both of the nuclei and of the protoplasm of the cells was distinctly and sometimes markedly better than it was in salt, but this was most striking in the livers which underwent autolysis with some degree of rapidity.

One of the most noticeable differences between the appearance of the sections of these autopsy livers and the sections made from the livers of bled dogs was shown by the fact that the pieces of human liver were equally well preserved throughout. The nuclei of the cells in the center of the section stained quite as well as those about the periphery. Since the livers which contained most blood at autopsy resisted autolysis best, it was thought that the presence of clotted blood in the livers obtained at autopsy accounted for the difference in appearance between these tissues and the tissues obtained from bled dogs. This idea was strengthened when it was found that if dogs were killed and allowed to remain four to five hours before the liver was removed, practically the same appearance was obtained during autolysis as when autopsy material was employed. Thus, in one instance liver cell nuclei could be seen scattered throughout the piece of tissue after forty hours at 36.5° C. in salt solution, and in another instance after seven days in dog's serum.

That the presence of coagulated blood in the liver has such a marked influence in inhibiting autolysis is a point which should be borne in mind in the microscopical examination of tissues. It must be remembered that if an animal is bled to death autolysis of the liver, and probably of the other organs as well, takes place much more rapidly than when the animal is killed with the tissues full of blood.

These experiments confirm the observations of Baer and Loeb, Wiener, Schryver, Launoy and Wells and go to show that the presence of blood serum is capable of retarding in a marked degree autolysis of liver and kidney tissue.

No definite explanation has so far been given for this phenomenon. Baer and Loeb think that the action of the serum is not that of an antiferment directed against the enzymes of the liver cells. Wiener thinks that it is dependent upon the slightly alkaline reaction of the serum. Schryver offers no explanation, while Wells believes that it may be due partly to an anti-autolytic substance, partly to the alkalinity of the serum.

It might be suggested that the slow autolysis of liver in blood serum is due to the fact that the serum furnishes nourishment to the cells sufficient to prolong their life in this medium. This, however, is not a satisfactory explanation. In the first place, the tissues were kept in toluol, which is fatal to cell life. In the second place it could be shown that serum exerts some influence upon the liver which is perceptible after the tissue has been washed free of serum and allowed to remain in NaCl solution at 36.5° C. Liver tissue from a bled dog was kept in contact with dog's serum at 36.5° C. for nineteen hours, then transferred, after thorough washing, to .85 per cent NaCl solution, and allowed to remain twenty-four hours longer at 36.5° C. The treatment with serum is capable of inhibiting autolysis subsequently in salt solution, for after twenty-four hours' contact with salt solution nuclei were still excellently preserved about the margin of the tissue, while liver placed directly in salt solution showed complete loss of nuclei after twelve to eighteen hours. This suggests that the serum exerts some influence upon the cells, and that this may retard autolysis even after the tissue has been thoroughly freed of the serum itself.

Baer and Loeb state that blood serum even in very small quantities inhibits autolysis. This, however, did not seem to be true for the method of investigation which was used in the present series of experiments. Serum diluted one-half with .85 per cent salt solution or with distilled water gave practically the same results as whole serum. If the serum, however, was diluted four times with .85 per cent NaCl, its power to inhibit autolysis was definitely impaired. Plasmolysis, as judged from the firmness of the tissue and the amount of sediment in the flask, was retarded to almost as great a degree as with whole serum, but in sections the nuclei of the cells were not preserved much longer than they were in .85 per cent NaCl. The difference between whole serum and diluted serum was much more marked in a dilution of one to ten. In this solution the softening of the liver and the disappearance of the nuclei took place about as rapidly as with .85 per cent NaCl, while serum diluted ninety-nine times acted exactly like .85 per cent NaCl.

In reviewing the possible explanations for the action of the blood serum in inhibiting autolysis, it was of great importance to take into account the reaction of the serum. Rowland and Hedin,[13] Biondi,[14] Stookey,[15] and Wiener[16] have shown that autolysis of various tissues proceeds much more rapidly when the reaction of the medium is acid than when it is neutral, while Rowland and Hedin have found that the autolytic ferments of the liver, kidney, and lymph glands are almost inactive in an alkaline fluid. Magnus-Levy has demonstrated, besides, that during autolysis certain acids are produced which may be recovered from the fluid in which the tissue has been kept.

When various samples of serum used in these experiments were tested, slight variations in their reaction were found. Dog's serum was faintly alkaline to litmus, but neutral to phenolphthaleine. One specimen of human serum was found to be faintly alkaline to litmus, but acid to phenolphthaleine, for with this latter indicator it required .3 cubic centimeter of N/10 NaOH to neutralize five cubic centimeters of serum. The stock of horse serum which was used throughout the experiments was alkaline both to litmus and phenolphthaleine.

It was thought possible that though the reaction was not in itself sufficient to explain the marked inhibition of autolysis by blood serum, still the blood serum might have the power of neutralizing the acid formed during the autolysis. Jacoby[17] has suggested that a certain degree of autolysis proceeds in the body during life, but the products of autolysis are carried away or neutralized by the blood and thus the self digestion of the tissues is held in check. If this were true the medium might remain neutral and autolysis would proceed much more slowly in serum than in NaCl. This supposition was found to be entirely erroneous, for the serum in which the pieces of tissue were kept became acid both to litmus and to phenolphthaleine. Moreover, after thirteen days, as the following experiment shows, as much acid was formed in serum as in NaCl.

Exp. XXVI. Ten grams of dog's liver were put in forty cubic centimeters of NaCl and ten grams in forty cubic centimeters of dog's serum. The stoppered flasks were allowed to remain at 36.5° C. for thirteen days. At the end of this time ten cubic centimeters of the filtered NaCl, in an average of three readings, neutralized 3.9 cubic centimeters of n/10 NaOH, while ten cubic centimeters of the unfiltered serum neutralized 4.3 cubic centimeters of n/10 NaOH. Phenolphthaleine was used as an indicator. The very dark color of the fluids made it difficult to determine accurately the end reaction, but even though the readings are only approximately correct, they show quite conclusively that as much acid is formed in serum as in NaCl.

Blood serum was then neutralized or made acid with acetic and hydrochloric acid, and experiments made with this neutral and acid serum, with the acid alone, and with normal serum as a control. When serum was used to which an equal volume of 0.4 per cent of HCl was added, the power to delay autolysis was entirely destroyed. Occasionally both in the control acid and in the acidified serum the margins of the tissue were fixed by the acid, but the pieces of tissue became exceedingly soft and friable. Serum brought to such an acidity with HCl that ten cubic centimeters neutralized 1.1 cubic centimeters of n/10 NaOH preserved the tissue somewhat better than the control acid, ten cubic centimeters of which neutralized 1.2 cubic centimeters of n/10 NaOH. Finally, serum having such an acidity that ten cubic centimeters neutralized .7 cubic centimeter of n/10 NaOH prevented autolysis practically as well as untreated serum. In the serum of this reaction the liver tissue was very firm at the end of fifteen days and nuclei were seen after thirty-eight hours. Finally, pieces of liver were kept in sodium carbonate and were compared at various periods with pieces of liver kept in blood serum alone and blood serum made alkaline with sodium carbonate. These experiments showed that though sodium carbonate in .1 per cent and in .2 per cent solutions prevented autolysis to a certain extent, the degree of inhibition did not approach that of the normal untreated serum. The addition of sodium carbonate to the serum had practically no effect upon its action.

Exp. XXXVII. 6–20–'07. Operation, dog etherized, bled to death, liver removed 4 P.M., used 5.30 P.M.

TABLE II.

		17½ Hours.	42 Hours.	66 Hours.	13 Days.
NaCl.	Macroscopic.	Moderately soft.	Same.	Soft.	Soft.
	Microscopic.	Two or three nuclei about margin.	No nuclei; poor preservation of cells.	No nuclei; poorer preservation of cells.	
.1% Na_2Co_3.	Macroscopic.	Moderately firm.	Fairly soft.	Same.	Quite soft.
	Microscopic.	Narrow zone of nuclei about margin.	Few pale nuclei in boundary zone; very poor preservation of cells.	No nuclei; much dissolution.	
0.2% Na_2Co_3.	Macroscopic.	Moderately firm; no peripheral zone on section.	About same.	About same.	Quite soft.
	Microscopic.	Nuclei well preserved about margin and far into tissue.	Very few pale nuclei about margin; cells show some dissolution.	No nuclei; cells show much dissolution.	
Dog's serum.	Macroscopic.	Quite firm.	Very firm.	Quite hard; much firmer than liver in .1% and .2% Na_2Co_3.	Very firm.
	Microscopic.	Wide zone of nuclei about margin.	Many nuclei about margin staining well in places; excellent preservation of cells.	Few very faint nuclei about margin; fair preservation of cells.	
Dog's serum + ½ .2%. Na_2Co_3.	Macroscopic.	Moderately firm.	Very firm.	Very firm.	Very firm.
	Microscopic.	Wide zone of nuclei about margin.	Many nuclei staining well; cells excellently preserved.	No nuclei; preservation of cells not quite so good as with serum untreated.	

In another set of experiments the effect of Ringer's solution and of various concentrations of NaCl were tried. With Ringer's solution the nuclei of the liver cells in some specimens remained a few hours longer than in salt solution and plasmolysis did not take place quite so rapidly. In one instance a few pale nuclei could be seen after forty-eight hours at 36.5° C., whereas, as in the control livers kept in salt solution, the nuclei had entirely disappeared after this period of time. In other specimens there was no apparent difference between Ringer's solution and 0.85 per cent salt solution. Sodium chloride was then tried in 0.1 per cent, 0.4 per cent, 1.2 per cent, and 2.0 per cent solutions, but the results were practically the same as with 0.85 per cent NaCl.

Since it was impossible to reproduce the results obtained with blood serum by the use of Ringer's solution and various concentrations of NaCl, other fluids were used to test the specificity of the action of the dog's serum. Heterologous dog's serum, horse serum, and human blood serum were substituted for homologous dog's serum, and it was found that all these sera acted in about the same manner. If there was any difference it was in favor of horse serum, for in a few specimens many more nuclei stained in the dog's livers kept in horse serum than in homologous and heterologous dog's serum or human serum. Egg albumen, moreover, undiluted and diluted one-half with salt solution, was found to retard autolysis very markedly. The results equalled those obtained with horse serum. Finally, two colloidal substances were employed, gelatin and agar. Gelatin in five per cent solutions and in 2.5 per cent solutions were made up in NaCl, and neutralized to litmus. In five per cent solutions the pieces of tissue remained almost as firm as in blood serum. The disappearance of the nuclei took place more slowly than in NaCl and Ringer's solution, but was somewhat more rapid than in blood serum. In 2.5 per cent solutions the nuclei disappeared almost as rapidly as they did in NaCl, but the plasmolysis was slow and the tissue remained almost as firm as it did in blood serum, though after fifteen days it began to soften. Agar-agar was used in 0.05 per cent, 0.25 per cent and 0.5 per cent solutions. In 0.05 per cent solution the agar is fluid, in 0.25 per cent solution it is rather thick, but still may be measured in a pipette, while in 0.5 per cent solution the agar is semi-solid and lumpy. The reaction is neutral to phenolphthaleine. The nuclei of the liver cells disappear quite as rapidly in these various agar solutions as in salt solution, but plasmolysis is much slower, particularly in the 0.5 per cent solution. From these experiments it would seem that egg albumen prevents the disappearance of the nuclei and plasmolysis of the cells quite as well as blood serum. Gelatin in five per cent solutions will delay to a certain degree the disappearance of the nuclei of the cells, whereas gelatin in less concentrated solution and agar, in the solutions employed, will not prevent the disappearance of the nuclei but will inhibit plasmolysis. It will also be remembered that as blood serum is diluted its power to preserve the nuclei of the liver cells is lost before the property of preventing plasmolysis disappears.

The effect which heat was found to have upon the serum differed somewhat from the results of Baer and Loeb. Serum subjected to a temperature of 65° C. for fifty minutes acted like unheated serum. If, however, the serum was heated to higher temperatures its properties were definitely altered. Blood serum was diluted one-half with NaCl or water and heated twenty minutes to one-half hour at 85° C. At this temperature dog's serum becomes opaque and semi-solid, while horse's serum forms a soft coagulum. In this heated serum the liver remains quite firm, almost as firm as it does in unheated serum, but the nuclei disappear much more rapidly. In one specimen the nuclei were gone at the end of sixteen hours, in another a few nuclei were faintly visible at the end of fourteen hours, but had disappeared at the end of thirty-eight hours. In the control serum, prepared in exactly the same manner except for the fact that it was unheated, nuclei were quite well preserved in the first specimen at the end of forty hours, and in the second at the end of thirty-eight hours. Further, it was found that heat had practically the same effect upon egg albumen. In heated egg albumen the power to prevent plasmolysis was but slightly impaired, whereas the property of preserving the nuclei was almost entirely lost. The injurious effect of heat upon the serum may be due to the destruction of some substances in the serum, or again it may be due to the changes which are brought about in its physical properties.

SUMMARY.

The experiments show that blood serum as compared with NaCl is capable of preventing softening and plasmolysis of liver tissue to a great extent, and of delaying the disappearance of the nuclei of the cells of the liver and kidney when these tissues are kept at 36.5° C. The action of blood serum cannot be reproduced by the use of Ringer's solution or of various concentrations of salt solution. Though blood serum will not inhibit autolysis when the serum is made one-tenth to two-tenths per cent acid, the property of normal serum is neither dependent upon its reaction nor upon the possible neutralization of acids formed during autolysis by the serum; for blood serum which is neutralized or made faintly acid, will inhibit autolysis practically as well as unheated serum and as much acid is formed during autolysis in blood serum as in NaCl. While alkalis inhibit autolysis to a certain extent, Na_2CO_3, even in a strength of two-tenths per cent, will not give the same results as blood serum. This quality of blood serum manifests itself only when the serum is used in great strength. By diluting the serum the power to prevent autolysis soon disappears; and the property of preserving the nuclei is lost before the power to prevent plasmolysis goes. A temperature of 85° C. destroys the ability of the serum to preserve the nuclei of liver cells almost completely, but injures the power of preventing plasmolysis very slightly. This action of blood serum is not specific for dog's liver. It is present in various samples of dog's serum, in horse and human serum, in egg albumen and to a slight extent in five per cent solutions of gelatin. Five-tenths per cent solutions of agar-agar do not inhibit autolysis of the nuclei of liver cells, but prevent plasmolysis to a certain extent.

REFERENCES.

1. Baer and Loeb. Arch. f. Exp. Path. und Pharmak., 1905, liii, 1.
   Baer and Loeb. Arch. f. Exp. Path. und Pharmak., 1906, lvi, 68.
2. Wiener. Cent. f. Physiol., 1905, xix, 349.
3. Schryver. Biol. Journ., 1906, i, 123.
4. Launoy. Compt. Rend. de la Soc. Biol., 1906, lxi, 496.
5. Wells. Journ. of Med. Research, 1906, xv, 149.
6. Hahn. Berl. Klin. Wochen., 1897, xxxiv, 499.
7. Landsteiner. Cent. f. Bakt. und Parasit Rund., 1900, xxvii, 357.
8. Glaessner. Hofmeister's Beitr., 1904, iv, 79.
9. Cathcart. Journ. of Physiol, 1904, xxxi, 497.
10. Oppenheimer and Aron. Hofmeister's Beitr., 1903, iv, 279.
11. Levene and Stookey. Journ. of Med. Research, 1903, x, 217.
12. Opie. Journ. of Exp. Med., 1907, ix, 207.
13. Rowland and Hedin. Zeit f. Phys. Chemie., 1901, xxxii, 341 and 531.
    Hedin. Journ. of Physiol., 1904, xxx, 155.
14. Biondi. Virch. Arch., 1896, cxliv, 496.
15. Stookey. Journ. of Med. Research, 1903, x, 212.
16. Wiener. Loc. cit.
17. Jacoby. Zeit. f. Physiol. Chemie, 1900, xxx, 149.

CONGENITAL OBLITERATION OF THE BILE DUCTS WITH CIRRHOSIS OF THE LIVER.*

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My attention was first directed to the study of this condition by Dr. J. P. C. Griffith sending to me for examination the liver obtained from an infant dying at the age of six months. The necropsy was limited to the removal of the liver and it was received by me with only the slightly dilated hepatic portions of the bile ducts attached. However, the clinical course and the changes in the liver were of such a nature as to make it permissible to consider the case, on the basis of probabilities, one of congenital obliteration of the bile ducts with cirrhosis of the liver.

The infant when born was a normal twelve-pound baby. From birth it had been deeply jaundiced, the stools clay colored and the urine deeply pigmented. Shortly after birth the child lost in weight but later gained. The infant was brought to the University Hospital to the service of Dr. Griffith, to whom I am indebted for permission to publish these notes, when it was five months old. On admission it was a somewhat emaciated infant, deeply jaundiced, with a few small purpuric spots on the scalp. The liver extended from the fifth rib to three centimeters below the costal margin in the mid-clavicular line. The spleen extended two and one-half to three centimeters below the costal margin. The urine, aside from showing a large amount of bile, was normal. The examination of the blood showed three million nine hundred thousand red corpuscles, fourteen thousand leucocytes and sixty-eight per cent of hemogloblin. An examination of the feces for bile pigment was negative. The temperature varied between 98° and 100° F. until a few days before death when it varied between 98° and 103° F. About a week before death a large blood-filled cyst developed above the right ear. With progressive loss of weight and strength the child died at the sixth month of life.

At necropsy the liver was found to be dark green, large

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and firm and the surface irregular. On cross section, minute streaks and bands of gray were seen running in various directions throughout the substance. On microscopic section there was seen to be an extensive increase in the perilobular connective tissue with proportionally great multiplication of bile canaliculi. In a number of areas as many as twenty to thirty of these canaliculi could be counted in the connective tissue about the periphery of one lobule. Here and there the connective tissue invaded the lobules, but it was in general confined to the periphery. The connective tissue within the lobules was of a younger and more cellular type than that about the periphery. Many of the small intrahepatic bile ducts were distended and there was extensive deposit of bile pigment within the liver cells and connective tissue, somewhat more marked in the center of the lobules than on the periphery.

As far as I have been able to determine, the first record in the literature of this condition is by Cheyne, who, however, apparently slightly misinterpreted the findings. In his essays on "Diseases of Children," published in 1801, he speaks of "an original and incurable malconformation of the liver," which "malconformation is probably an impermeable thickening of the beginnings of the hepatic ducts or, as they are called, the Pori Biliarii." Since then a number of instances of the condition have been recorded and several more or less exhaustive treatises have been written upon the subject, the most notable being those of Thomson,[35] Giese,[16] and Skormin.[31] Though there have been variations in the degree of the cirrhosis found and variations in the localization of the biliary obstruction in the different cases, there is comparative uniformity of opinion as regards the clinical picture and the gross and microscopic pathological findings. The subjects are always deeply jaundiced either from birth or from a day or two later, the stools remain clay colored, and the urine deeply pigmented. Frequently the child remains well nourished for a considerable time and the bodily functions are performed in a manner strikingly out of harmony with the severity of the actual lesion. At times, and especially has this been so in the cases reported in the early part of the past century, hemorrhages from the umbilical cord or from other portions of the body have been noted. Cheyne interpreted this association of jaundice and bleeding according to our present view as shown by his statement: "The bleeding proceeded from the unhealthy change produced in the blood by the reception of the bile into the mass of fluids." Frequently the large, hard liver can be felt as well as at times its uneven surface. The spleen is usually enlarged; at times ascites is present. The child dies usually before the eighth month; only three cases amongst the sixty-two that I have collected from the literature exceeded this limit, two living until the ninth month and one until the eleventh month. The pathological changes in the liver are those of a multilobular and monolobular cirrhosis with some intralobular involvement and a marked multiplication of bile canaliculi.

As regards, however, the actual cause of the condition, whether the primary lesion is that of the bile ducts or that of the liver, whether the changes in the ducts are due to a developmental anomaly or to the organization subsequent to an inflammatory process, great difference of opinion prevails. It is this phase of the subject that has especially appealed to me and is the one to which I shall devote the remainder of my remarks.

We shall consider firstly the question as to whether the condition is primary in the liver or in the bile ducts, and, if possible, come to some conclusion. Rolleston[80] is the most ardent supporter of the view that the cirrhosis is the primary condition induced by some poison being excreted by the liver and setting up in that organ a cholangitis that subsequently descends to the larger bile ducts and there sets up an inflammation that later leads to organization. In favor of his view he presents the following four arguments:

(1.) "The almost constant occurrence of cirrhosis in these cases of bile duct obstruction in infants as compared with the infrequency and irregularity with which cirrhosis follows obstruction of the larger bile ducts in later life." As to the alleged infrequency of the occurrence of cirrhosis in adults consequent upon biliary obstruction, Mangelsdorf,[81] in 1882, collected one hundred and eighty-four cases of this condition, and in 1901 Ford[82] added twenty-four to this series. The obstruction in most of these cases was the result either of calculi or carcinoma of the pancreas or bile ducts. How many more cases have never been accorded the dignity of a report we cannot calculate, for so soon as a condition has been observed frequently enough for two hundred or more instances to have been reported, it is no longer of sufficient interest to warrant an individual report. Moreover, if the bile duct obliteration is secondary to the cirrhosis, why do we not find more frequently in adults obstruction of the ducts secondary to a Hanot's cirrhosis, a condition in adults essentially the same as that claimed by Rolleston to be the primary condition in children, namely, a descending cholangitis? A feature that impresses me as being of significant importance in this connection is the fact that in twenty-four (1, 10, 11, 13, 20, 23, 24, 25, 26, 29, 33, 34, 35, 38, 39, 42, 43, 44, 48, 50, 51, 54, 58, 59) of the sixty-two cases that I have collected, the obstruction was in the duodenal portion of the ducts and the hepatic portion was patulous, whereas, in only ten of the cases (3, 12, 17, 19, 22, 36, 45, 47, 56, 60) was the obstruction more marked in the hepatic end than in the duodenal end. If this obstruction were the result of an extension of inflammation from the liver it would be most natural for the involvement to be in those portions of the ducts nearest to the liver rather than in those portions farthest removed from it. Again, there have been cases of obliteration of the ducts in those dying very shortly after birth and in which, as far as the organ was described, only the earliest stages of cirrhosis of the liver have been found (1, 4, 8, 12, 23, 26). The only rational deduction that I think can be drawn from the association of these three facts, obstruction, early death, and little cirrhosis, is that the biliary stasis had not existed long enough to have produced more advanced changes. Rolleston admits in regard to Ross's[73] case that the evidence points in favor of the lesion in the duct being primary, but says that in the other cases as far as one can judge fibrosis in the liver is quite as old as the lesion in the bile ducts. How one can judge of the relative ages of advanced fibroid change in two structures so totally different in function and morphology as the liver substance and the bile ducts is beyond my comprehension.

(2.) Rolleston's second point in favor of the cirrhosis being primary is the large size of the liver, resembling hypertrophic biliary cirrhosis. It is true that the livers of hypertrophic cirrhosis and obstructive cirrhosis resemble each other in size, but it is also true that the livers in cases of cirrhosis known to be due to biliary obstruction are large. Let me quote Ford's statement which is based on the one hundred and eighty-four cases reported by Mangelsdorf and the twenty-four cases collected by himself: "The livers in these cases of obstructive cirrhosis are greatly enlarged with a rough jaundiced surface and considerable perihepatitis." Very late in the process it is possible to have a decrease in the size of the organ in these cases of obstructive cirrhosis as in practically every other hypertrophic process in the liver, but the majority of cases of congenital obliteration do not live long enough for contraction to result.

(3.) Rolleston's third argument is "the large size of the spleen, a phenomenon not met with in uncomplicated biliary obstruction." This statement is undoubtedly correct but it can scarcely be construed as having any bearing on the subject under discussion, for these cases are practically all complicated by hepatic cirrhosis, and as Rolleston[103] himself says in discussing cirrhosis resulting from biliary obstruction in the adult, "the spleen is sometimes small or of normal size, but in cases where considerable fibrosis of the liver co-exists with obstruction of the larger ducts, as in Weber's cases, there may be very considerable enlargement, though not to the same degree as in hypertrophic biliary cirrhosis."

(4.) The fourth point Rolleston presents in favor of his view is "the fact that in some instances several cases of this rare disease have occurred in the same family." He does not mention the cases to which he refers. In a thorough search through the literature I have been able to find but one instance in which more than one member of a family was shown by autopsy to have had an obliteration of the ducts. This was in a report by Binz[4] of two brothers, one dying when twenty-four hours old and the other on the second day. In both of them the cystic, hepatic, and common ducts were transformed into an irregular fibrous mass entirely without lumina. In the first case the liver was reported as being slightly enlarged and soft; the only note of the liver in the second case was that the capsule was thickened. The father was supposed to have had syphilis, and it is not improbable that both cases were instances of congenital syphilis. West[56] has reported one case dying of congenital obliteration of the bile ducts in which other children of the same mother were supposed to have died of the same condition, but there were no autopsies to support this supposition. A second case reported by West,[56] one of a number of sisters and brothers dying as claimed of congenital obliteration of the bile ducts, has insufficient data to warrant this diagnosis, and on the other members of the family no autopsies were performed. Thomas[54] reports a case of congenital obliteration in a child dying on the twelfth day; four other children of the same parents died before the ninth day of life, all jaundiced. Though Thomas assumes that they all died of the same condition, there were no autopsies to confirm his view. A few other instances, those of Arkwright,[53] Blomfield,[54] and Pearson,[55] have been reported in which several infants in one family have died with jaundice, but they had few, if any, of the symptoms of biliary obstruction and no autopsies were performed, so that when one considers the numerous causes of jaundice and subsequent death in childhood it is scarcely necessary to state that we cannot include these cases, however suggestive some of them may be, in the present consideration.

Furthermore, if we consider the cirrhosis to be primary and caused by he circulation through the liver of substances irritating to it, would it not be rational to look for inflammatory lesions, the result of the same irritating substance in other organs? Such lesions have not been recorded in any of the autopsies on these cases. Moreover, as Rolleston himself admits, as speaking against his view, it would also be expected that the mother would give some evidence of the circulation of these toxic substances through her own organs.

With the presentation of the above facts, I think we are justified in considering that there is little or no support of the view that the obstruction is secondary to a cirrhosis In support of the claim that the obstruction is the primary condition, and the cirrhosis a result of the ensuing biliary stasis, is the great weight of evidence that in both adults (Mangelsdorf[81]) and children (Ford[8]) biliary stasis has resulted in the same chain of events and the same pathological findings as are presented in these cases. Furthermore, the work of Steinhaus,[86] Pick,[87] Lannaeq,[88] Gerhardt,[89] Beloussow,[90] and Harley[91] showed in experimental obstruction in animals the same changes in the liver as are found in these cases of biliary stasis in human individuals.

Let us now see if we can determine the nature of these lesions in the ducts that give rise to the ensuing changes. The possibilities to be considered as causing the obliteration are primarily three: 1st, a developmental anomaly; 2d, the organization of a non-specific intrauterine inflammatory condition located in the ducts themselves, and 3d, a syphilitic induration of the ducts.

1. An anomaly of development. — A number of facts speak strongly for an anomaly of development being the causal factor in many of the cases. Firstly, the fact that the bile ducts are originally solid cords, Remak's fibers, as they are called, and that subsequently these have lumina formed within them suggests that obliteration may be the result of a simple failure of lumination in some portion of the biliary tract. According to Hertwig, quoted by Mohr,[41] the earliest fetal evidence of the liver and ducts is a solid cord that grows out from the gut tract about the third week. The

peripheral end of this branches to form the bile capillaries while the proximal end forms the hepatic duct. After a short time this entire mass detaches itself from the gut tract and lies free in the abdominal cavity. Some time later a second budding takes place from the gut tract to form the ductus choledochus which grows outward to join the ductus hepaticus already formed. This is a very suggestive fact, for in some of the cases (6, 16, 32, 46, 55) the obliteration was just at the point of junction of the hepatic and common ducts, the portions above and below this point being patulous. It seems plausible that the obliteration may have resulted from a faulty union of the two rudimentary portions of the ducts.

A feature lending even more weight to the view that an anomaly of development may be the cause of the condition under discussion is the occurrence of other undoubted anomalies of development in the liver and its appendages and the occasional occurrence of impervious ducts associated with striking congenital defects in other portions of the body. In the first group are such cases as those of Simpson[68] in which the gall bladder, the cystic duct, and the caudate and Spigelian lobes were all found absent. Simple congenital absence of the gall bladder as noted by Morgagni, Wahlbom and Büttner (quoted by Meckel[92]), Förster[93] and others is a not unusual occurrence. Eshner[94] collected a number of instances of this condition and reported one of his own.

In the second group are such cases as that of Feer[14] in which there was complete situs inversus associated with obliteration of the ducts; that of Witzel[95] in which there was obliteration of the ducts, situs inversus, cystic liver, cystic kidneys, absence of both eyeballs and other minor defects; and the case of Herbert[96] in which there was a persistent ductus Botalli and absence of the hand and ulna of the left arm associated with obliteration of the ducts. The association of these marked anomalies of development with impervious ducts is to my mind a feature of great significance and leads me to believe that a large percentage of the cases of congenital obliteration are a result of a congenital defect of development.

2. The organization of a non-specific inflammation of the ducts. — In regard to this possibility it is difficult to say much on the basis of observation on account of the fact that these cases present themselves for study only long after the manifestations of an acute process would have been replaced by the fibroid changes which are not characteristic of any particular form of inflammation. Wronka[62] believes that the force and rapidity with which bile is expelled from the ducts in difficult labors may produce irritation and inflammation, and reported a case of an icteric infant dying on the eighth day in which the autopsy revealed a hemorrhagic-diphtheritic inflammation of the bile ducts. However, most of these cases undoubtedly have their origin a considerable time before birth. In Virchow's Archiv for 1867 four cases were reported in which simple catarrhal inflammation of the bile ducts was supposed to have caused a partial fibroid obliteration of them. Nevertheless, the relative infrequency of catarrhal jaundice in infants compels us to look upon inflammation of the ducts with subsequent organization as an improbable cause of the obliteration in the majority of cases, though it is possible that in intrauterine life the ducts are subject to some influences not present after birth.

3. Syphilis. — In a review of the cases appearing in the literature it will be observed that there are a number of syphilitic conditions affecting the liver and gall ducts simulating the one under discussion. Thus Lommer[35] reports a case of a macerated syphilitic fetus born dead in which the ductus choledochus was transformed into a fibrous cord and the right lobe of the liver was the seat of a syphilitic hepatitis. Schüppel's[69] third case was similar; the portal vein, hepatic artery, and hepatic duct of an infant dying on the ninth day were involved in a dense syphilitic infiltrating mass that extended into the liver. The cases of

Beck[97] and Chiari[98] showed a gummatous infiltration of the bile ducts with more or less constriction resulting, but no involvement of the liver. Again, there have been cases such as those of Hansemann,[99] Neumann,[100] d'Espine and Picot,[101] and Henoch[102] in which the livers have resembled biliary cirrhosis without obstruction, but have been thought by their observers to be due to an interstitial syphilitic hepatitis. In some of the cases (Neumann[63] and Ashby[3]) there has been a history of parental syphilis, but none of the stigmata of congenital syphilis in the infants. Two of the reporters of cases (Skormin[51] and Roth[50]) though presenting no basis for their view held syphilis accountable for the bile duct obliteration in their cases. I can see no rational basis for looking upon the condition as syphilitic, when the numerous, definite lesions of congenital syphilis are lacking.

Lastly, it is worthy of mention that a striking simulation of obliteration of the bile ducts can be conceived of in a condition such as was presented by Ford's[82] case: the patient was an infant with tuberculosis of the cervical lymph glands, developing at the age of one and one-half years deep jaundice, with clay-colored stools and pigmented urine. Later the liver became enlarged, and at autopsy a typical biliary cirrhosis was found as the result of an inflamed gland at the hilus of the liver pressing upon and completely obstructing the common duct. This case, furthermore, adds convincing evidence of the secondary nature of the cirrhosis in obstruction of the ducts, as the microscopic changes in the liver were identical with those found in congenital cases.

Let me add a word in regard to the use of the term "congenital obliteration of the ducts." Though I have used this term throughout my remarks, I believe that it does not most accurately express the existing condition. The word "obliteration" presupposes the existence of a lumen which subsequently becomes destroyed. As it is my belief as presented in the above analysis that the condition is in most cases the result of an anomaly in which there is a failure of formation of a lumen rather than a destruction of it, I believe that the term "atresia of the bile ducts" would better express the existing condition.

Treatment. — As will be readily appreciated from an understanding of the condition of the bile ducts in these cases medical treatment is valueless. Surgical intervention may in suitable cases give some hope, for if the obstruction is low in the ducts a rational procedure would be to form an anastamosis between some portion of the small intestine and the upper, patulous portion of the ducts. Operation was unsuccessful in the cases of Putnam,[47] Giese,[19] and Morse and Murphy.[43] Nevertheless, since the outlook without operation is absolutely hopeless, and operation can be of service in suitable cases, one would be justified in resorting to this measure.

CONCLUSIONS.

1. In the congenital condition of which the two most prominent features are an obliteration of some portion of the bile ducts and a more or less extensive degree of cirrhosis of the liver, the obliteration of the bile ducts is the primary condition and the cirrhosis a result of the ensuing biliary stasis.

2. In the majority of instances the obliteration of the ducts is the result of an anomaly of development, a failure of the formation of a lumen.

3. The term "atresia of the bile ducts" better expresses the existing condition than "obliteration of the bile ducts."

The following are the references to those cases which from the data presented are apparently true instances of congenital obliteration of the bile ducts:

1. Anderson. Boston Med. and Surg. Jour., 1850, xli, 440.
2. Ashby. Pendelbury Hosp. Abstracts, 1886, 73.
3. Ashby. Arch. Pediat, 1884, i, 537.
4. Binz. Virchow's Archiv., 1886, xxxv, 360.
5. Binz. Ibid.
6. Binz. Ibid.
7. Blundell. Elliotson's Human Physiology, 1840, 101.
8. Campbell. Northern Jour. of Med., 1844, i, 237.

9. Campbell. Ibid.
10. Cursham. Lond. Med. Gaz., 1840, xi.
11. Danforth. Chicago Med. Jour., 1870, 110.
12. Dean. Trans. Amer. Med. Ass., 1858, xi, 304.
13. Donop. De Ictero Speciatim Neonatorum. Dissert., Berlin, 1828.
14. Feer. Verhandl. d. xx. Vers. d. Gesell. f. Kinderh., 1903.
15. Fruend. Jahrb. f. Kinderh., 1876, ix, 178.
16. Fuss and Boye. Virchow's Archiv., 1906, clxxxvi, 288.
17. Gessner. Ueber kongenit. Verschluss d. gross. Galleng. Dissert., Halle, 1886.
18. Gibbs. Trans. of the Path. Soc. of Lond., 1883, xxxiv, 129.
19. Giese. Jahrb. f. Kinderh., 1896, 252.
20. Glaister. Lancet, 1879, ix, 293.
21. Gould. Boston Med. and Surg. Jour., 1855, 109.
22. Gould. Ibid.
23. Griffith. Arch. Pediat., 1905, xxii, 257.
24. Harley, Diseases of the Liver, 299.
25. Hawkins. Trans. of the Path. Soc. of Lond., xlvi, 76.
26. Hennig. Jahrb. f. Kinderh., 1876, ix, 406.
27. Henoch. Lehrb. d. Kinderh., 9th ed., 25.
28. Heschl. Wiener. Med. Woch., 1865, No. 29.
29. Hobson. Trans. of the Path. Soc. of Lond., 1881, xxxiii, 183.
30. Knopf. Münch. Med. Woch., 1891, Nos. 16 and 17.
31. Knopf. Ibid.
32. Kynoch. Edinb. Med. Jour., 1896, xvii, 35.
33. Legg. Lancet, 1877, i, No. 16.
34. L'Hommeau. Bull. Soc. Anat. de Paris, 1842, xvii, 52.
35. Lommer. Virchow's Archiv., 1885, xcix, 130.
36. Lotze. Berl. Klin. Woch., 1876, 30.
37. Lugenbühl. Verhandl. d. xx, Vers. d. Gesell. f. Kinderh., 1903.
38. Menzies. Australasian Med. Gaz., 1904, 20.
39. Meyer. Berl. Klin. Woch., 1886, 255.
40. Michael. Ref. in Archiv. f. Kinderh., vii, 2, 137.
41. Mohr. Ein Fall von Kongenitalem Icterus. Dissert., Berl., 1898.
42. Morgan. Trans. of the Path. Soc. of Lond., xxix, 137.
43. Morse and Murphy. Boston Med. and Surg. Jour., 1907, clvi, 102.
44. Murchison. Clinical lectures on diseases of the liver, 1868, 363.
45. Nunley. Trans of the Path. Soc. of Lond., 1872, xxiii, 152.
46. Parker. Lancet, 1901, ii, 520.
47. Putnam. Archiv. Pediat., 1898, 663.
48. Rolleston and Hayne. Brit Med. Jour., 1901, i, 758.
49. Romberg and Henoch. Klin. Wahrnehm. u. Beobachtung., 1851, 158.
50. Roth. Virchow's Archiv., 1868, xliii, 296.
51. Skormin. Jahrb. f. Kinderh., 1902, lvi, 196.
52. Smith. Diseases in children, 3d ed., 718.
53. Stevens. Arch. Pediat., 1896, xiii, 733.
54. Thomas. New Zeal. Med. Jour., 1891, 161.

55. Thomson. Congenital obliteration of the bile ducts.

56. West. Lectures on Diseases of Infancy and Childhood, 1874, 623.

57. Westerman. Jahrb. f. Kinderh., 1904, 518.

58. Westerman. Ibid.

59. White Amer. Jour. of Obstet., 1888, 48.

60. Wilks, quoted by Leyden. Beiträge z. Pathol. des Icterus, 1866, 183.

61. Wollstein. Arch. Pediat., 1902, xix, 189.

62. Wronka. Bieträge z. Kentniss. d. Angeborn. Leberkrankh. Dissert., Breslau, 1872.

The following are references to such cases as by reason of insufficient or incomplete data or contradictory findings cannot be classified as true instances of the condition:

63. Neumann. Berl. Klin. Woch., 1893, xxx, 445.

64. Oxley. Lancet, 1883, ii, No. 23.

65. Brandenberg. Festschrift f. Hagenbach-Burckhardt, 1897.

66. Jenkins. Trans. Amer. Med. Ass., 1858, xi, 261.

67. Köstlin. Medicin. Korrespondenzbl. d. Württemb. ärzt. Vereins, 1862, xxxii, 105.

68. Simpson. Edinb. Med. and Surg. Jour, 1860, vi, 1045.

69. Schüppel. Archiv. d. Heilkunde, 1870, 74.

70. Still. Clin. Jour., 1901, xvii, 324.

71. Virchow. Ges. Abhandl., 858.

72. Smith. Trans. of Path. Soc. of Lond., 1890, xli, 154.

73. Ross. Lancet, 1901, i, 102.

74. Rolleston and Kanthack. Archiv. f. Klin. Med., 1892, 488.

75. Campbell. Loc. cit., Case 2.

76. Hennig. Loc. cit., Case 2.

77. Knopf. Loc. cit., Case 3.

78. Morse and Murphy. Loc. cit., Case 1.

79. Parker. Loc. cit., Case 2.

General References.

80. Rolleston. Diseases of the liver, 1905, 641.

81. Mangelsdorf. Deutsch. Archiv. f. klin. Med., 1882, xxxi, 522.

82. Ford. Amer. Jour. Med. Sc., 1901, cxxi, 60.

83. Arkwright. Edinb. Med. Jour., 1902, 156.

84. Blomfield. Brit. Med. Jour., 1901, i, 1142.

85. Pearson. Underwood's Diseases of children, 10th ed., 1846, 168.

86. Steinhaus. Archiv. f. Exp. Pathologie, 1891, xxviii.

87. Pick. Zeitschr. f. Heilk., 1890, xi.

88. Lannaeq. Archiv. de Med. experimentelle, 1897.

89. Gerhardt. Archiv. f. Exp. Pathologie, 1892, lxxx.

90. Beloussow. Archiv. f. Exp. Pathologie, 1881, xiv.

91. Harley. Brit Med. Jour., 1898, ii.

92. Meckel. Handbuch. d. Path. Anat.

93. Förster. Die Missbildungen des Menschen, 1865, 125.
94. Eshner. Med. News, 1894, lxiv, 548.
95. Witzel. Centralb. f. Gynek., 1880, 561.
96. Herbert. Rev. d. Orthoped., 1904, i, 57.
97. Beck. Prager-Med. Woch., 1884, No. 26–29.
98. Chiari. Prager-Med. Woch., 1885, No. 47.
99. Hansemann. Med. Centralanzeiger, 1893, No. 5.
100. Neumann. Berl. Klin. Woch., 1893, No. 19.
101. d'Espine and Picot, quoted by Lesage and Demlin. Rev. de Medicine, 1898, No. 1.
102. Henoch. Lehrb. d. Kinderkrank., 9th ed., 96.
103. Rolleston. Diseases of the liver, 331.

A NEW METHOD OF EXAMINATION OF THE FECES FOR THE OVA OF UNCINARIA. WITH REPORT OF A CASE OF U. AMERICANA AND OF A CASE OF U. DUODENALE.*

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Having very recently had two cases of Uncinariasis under observation, one U. Duodenale and the other U. Americana, and while making frequent examinations of the feces, it was noted that the ova of these parasites were quite sticky and that this peculiarity (as far as I know not mentioned in any description) could be made use of in searching for these ova.

The methods recommended for finding parasitic ova in the stools include (1) the examination of a small amount of feces mixed if necessary with water on a slide under the microscope; (2) the natural sedimentation of a thoroughly liquefied stool in a tall narrow glass jar and the removal after a few hours with a pipette of some of the middle strata of deposit at the bottom of the jar for microscopical examination; (3) the centrifugalization of a small amount of much diluted feces and the subsequent microscopic search of this sediment.

This latter method, when the washing is frequently repeated and when after each centrifugalization the supernatant dirty water is thrown away and fresh water added, the whole then being shaken up and again placed in the centrifuge, has proved most useful in my hands.

In this way all bacteria, free coloring matter, light vegetable matter, etc., is soon got rid of, and only the heavier particles, including any ova that may be present will remain. After about six repetitions of this eliminative washing, the sediment can be easily and satisfactorily examined under the

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low power of the microscope. There is then left no obscuring cloud of bacteria nor fine granular débris, but instead each ovum or muscle fiber or crystal or vegetable fiber stands out sharp and clear.

In endeavoring to remove some ova from a slide under the microscope prepared in this manner, by touching the egg with a very finely drawn out glass tube and thus causing it to be carried up into the tube by capillary attraction, it was found impossible with the ova of Uncinaria, the eggs having stuck to the glass. I have thus frequently transferred from one slide to another the ova of Ascaris Lumbricoides, of Trichiuris Trichiura and of Taenia Saginata and have never seen them adhere at all to the slide. A rather peculiar fact to be noticed in this connection is that the ova of the Uncinaria, although sticking closely to the glass slide, do not seem to adhere to any of the many other constituents of the stool. When a drop of this washed sedimented feces is allowed to stand on a slide for a few minutes and then gently immersed in water and examined microscopically, the eggs are found adhering to the slide while all else has been washed away. If additional drops are placed on the slide and washed off, the slide becomes thickly studded with the eggs as is shown in the accompanying photograph. A ring of asphalt may be used to keep the drop when placed on the slide in bounds and also serves to support a cover-glass. Both the old world and new world variety act in the same way. The ova at all stages in their development behave in the same manner even including those in which a living embryo could be seen moving within the egg. Ova were also seen to develop up to this stage while mounted in this way in water and under a cover-glass, but were not observed to progress further. For demonstration purposes this method has proved very useful.

It has been remarked by nearly all writers that it is much more difficult to find the ova of Uncinaria when the stools are loose than when they are formed and the explanation of this may lie in the fact that perhaps in loose watery stools the ova sink to the bottom, adhere to the vessel in which the stool is collected, and are thus not to be found in such large numbers in the feces examined.

On the other hand in loose watery stools or those containing mucus the eggs I observed did not adhere so well to the slide.

It is conceivable also that this stickiness might aid in the distribution of the ova, although this is very problematical.

The clinical report of two cases of Uncinariasis is added to demonstrate how widely spread this disease is, and how common it would probably be found to be if systematic examinations of the stools were made even in cities as far north as Philadelphia.

The first case illustrates the extreme value of routine laboratory examinations.

P. J. Italian. Aged twenty-six years. Admitted to the Philadelphia Hospital on 3–28–07. He had been in this country one year spending all of that time working as a laborer building bridges in Pennsylvania. About eight weeks before his admission to the hospital he began to grow weak and short of breath, and to cough and to have pain in his chest and abdomen. On exertion he had marked palpitation. In about a month he had to stop work and went to a hospital where he was in bed for some days and where he was found to have a left-sided pleural effusion which was tapped and about a quart of fluid removed. He then came to the Philadelphia Hospital with practically the same symptoms. The important points of the physical examination on admission were as follows: Fairly well nourished, anemic looking young man. Tongue, pale and moist. Pulse regular and of low tension. At base of left chest small area of almost complete flatness on percussion with loss of fremitus and distant breath sounds. The collodion dressing over the aspiration wound still in place. The spleen was distinctly palpable.

The patient's temperature during the first week he was in the hospital was always above 100° and below 103°, during the second week it was between 99° and 101°. A Widal test on 3–30–07 was negative, and on the same date the leucocytes numbered seven thousand per cubic millimeter; the differential leucocyte count showed normal proportions of the various forms.

4–5–07. The examination of the blood showed Hem. forty per cent. Red cells, two million one hundred and ten thousand. White cells, seven thousand.

On account of the persistence of the fever, and the enlargement of the spleen, and the increasing anemia together with the suspicious signs existing at the left base, an aspirating needle was introduced on that side, but no fluid was obtained.

4-10-07. The examination of the stools on this day cleared up the case at once. Ova of Uncinaria were found in large numbers. Ten of these eggs were carefully measured and were found to range between 61-78 μ in length by from 40-45 μ in breadth, the average size was 67.8 μ–42.4 μ. These measurements led to the mistaken idea that the worms were of the new world variety, or Uncinaria Americana, but on obtaining the worms themselves from the stools later all were found to be Uncinaria Duodenale. The comparative size of these eggs according to various authorities is here quoted:

U. Duodenale, 55–65 μ = 32–45 μ }
U. Americana, 64–75 μ = 30–40 μ } Braun.
U. Duodenale, 50–60 μ = 30 μ }
U. Americana, 68–70 μ = 38–40 μ } Smith.
U. Duodenale, 52–60 μ = 32 μ }
U. Americana, 64–76 μ = 36–40 μ } Porto Rico Anemia Commission.

A study of these figures will show why the diagnosis of Uncinaria Americana was made; and demonstrates the unreliability, in some cases at least, of determinations based on the size of the ova.

4-18-07. The patient was given Thymol gr. LX. and about twenty-five adult male and female worms were found in stools, all of these were Uncinaria Duodenale. During the next week Thymol gr. LX. was given on two occasions but only about six or eight worms were found. Eggs still continued in the stools.

14-29-07. Examination of the blood showed red corpuscles, one million seven hundred and forty thousand. White corpuscles, eight thousand four hundred.

5-11-07. Thymol gr. XC. was given and a number of worms were found, bringing the total number recovered from the stools to between fifty and sixty, all of which were U. Duodenale. After this the patient began rapidly to improve in weight and color, and would not remain longer in the hospital. There were still a few ova in his feces when he left on 5-15-07.

The second case, although the presence of Uncinaria had probably but a slight influence upon the patient's general health, is interesting from another standpoint. The abdominal symptoms in pulmonary disease are often confusing and led the surgeons who were called in to open the abdomen in spite of the medical diagnosis of pulmonary abscess.

J. F. Black. Aged twenty-six years. Waiter. Born in North Carolina. Admitted to the Philadelphia Hospital 2-27-07. Service of Dr. Stengel.

Had had chills and fever in 1901. Has been living in Philadelphia for last four years coming to this city from his home in North Carolina. On 2–25–07 had a chill followed by pain in right chest and then cough. On examination the patient was found to have consolidation of the right upper and lower lobe, with all the accompanying signs and symptoms of a croupous pneumonia. He became quite jaundiced. His urine and sputum were very bile tinged. His spleen was not palpable at this time. His pulse was very weak and irregular and altogether the attack was a very severe one. On 3–4–07, the seventh day after the initial chill, the temperature dropped and the patient became much more comfortable and was apparently out of danger. The temperature remained normal until 3–10–07, when it rose suddenly to 102 , and then dropped quickly to normal and the patient that day complained of pain in right axilla, also on 3–11–07 there were two abrupt elevations of temperature and again on 3–20–07. No explanation could be found at the time for these rises. On 3–24–07 his temperature was around 104° all day but was normal on the 25th, and the patient was then found to have chicken-pox; his temperature reached 105° on the 26th. Having recovered from the chicken-pox he left the hospital on 4–2–07.

He reëntered the hospital on 5–14–07, not having been very well since he left; complaining of cough, pain in chest and abdomen and extreme weakness. On examination an area of dulness was found still to be present at base of right lung, with harsh breathing and subcrepitant and bubbling râles. Repeated examinations of the sputum revealed no tubercle bacilli but showed enormous numbers of streptococci, staphylococci and other organisms. A blood culture was negative.

On 5–18–07 the ova of Uncinaria were found in small numbers in the stools. These ova averaged in length 71.5 μ by 37.8 in width and were therefore thought to be from Uncinaria Americana, which was subsequently proved to be the case at the autopsy.

On 5–22–07. Thymol gr. LX. given, but no worms were recovered from the stools. The patient's condition did not warrant another attempt to dislodge the worms.

During this time the patient had a typical hectic temperature ranging daily from 98° or 99° to 103°.

A blood count on 5–17–07 showed three million three hundred and eighty thousand red cells and thirteen thousand three hundred and thirty white cells with eighty-four per cent neutrophiles.

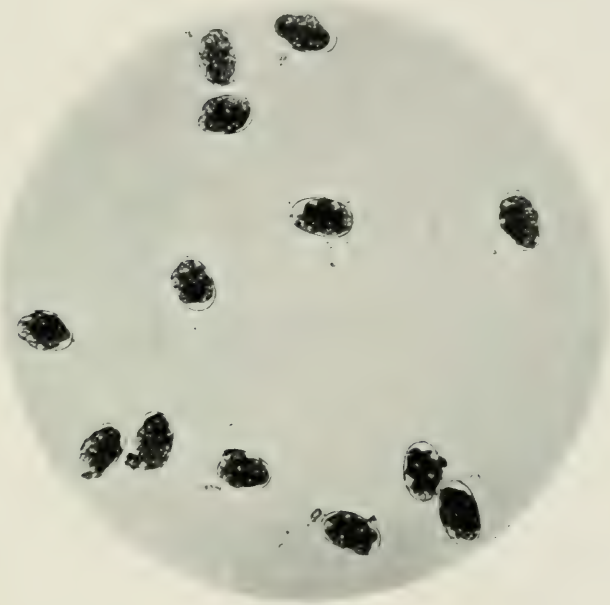
The patient grew weaker, the spleen became enlarged, the signs at the base of the right lung increased, the dulness was not movable, the tactile fremitus and vocal resonance were not lost, and there were no signs of free fluid in the pleural cavity. The abdomen became slightly swollen, tender and rigid, but nothing abnormal could be detected on palpation.

On account of the hectic temperature, leucocytosis, enlarged spleen, increasing weakness, absence of tubercle bacilli in the sputum, taken in consideration with the signs at the base of the right lung, the diagnosis of pulmonary abscess or interlobular empyema was made. The case was transferred to the surgical wards on 5-29-07 with the request that should the man be thought strong enough and the signs sufficient that the right chest be opened and any purulent collection evacuated and drained. The patient was operated upon the same day. The surgeons, however, thinking the pulmonary signs indefinite and the abdominal ones positive, first introduced an aspirating needle into the right pleura, and not getting any fluid proceeded to open the abdomen under local anesthesia over the gall bladder region. Nothing was found but a small amount of clear fluid in the abdominal cavity so the wound was closed. The patient died five days later.

The intestines and the right lung were removed through the abdominal incision twenty-four hours after death. The lung was bound to the chest by slight easily torn adhesions, the lower lobe had running across it a raised ridge about three inches in length by one inch in breadth, looking like a welt on the skin raised by a very sharp blow of a stick. The crest of this ridge had evidently been adherent to the costal pleura and was yellowish and somewhat ulcerated. On section this area was found to be fairly firm, free from air and beginning to disintegrate and break down. The cause was found to be a large thrombus in one of the large arterial branches supplying this portion of the lung.

Sections from this area, examined microscopically, showed entire disappearance of lung tissue, a mass of round cells and in the center granular débris. Liquefaction was apparently just beginning.

On opening the intestines ten Uncinaria Americana were found, eight of these were females and two males. All were dark in color, were alive, and were not adherent to the mucous membrane. They were found only in the small intestine between one and two yards below the pylorus.



Ova of Uncinaria duodenale. Collected from the feces by the author's method, adhering to glass slide even after gentle washing.

CONTRIBUTION TO THE DIFFERENTIATION OF BACILLUS COLI COMMUNIS FROM ALLIED SPECIES IN DRINKING WATER.*

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It is not the purpose of this article to deal with the old and controversial question of the significance of B. coli communis as an indication of pollution in drinking water, nor to go into details of the typical or atypical biological characteristics of the organism; but especially to determine a constant biological feature by which it can be differentiated with certainty from the allied species of the colon group. It is common knowledge that B. coli communis presents such extensive variations that often cultures isolated from water and reported as identical with this microörganism will, if studied more closely, be found to have very little or no relation at all with it. The assumption that perhaps the acceptance of such variations in B. coli communis is responsible for the unsatisfactory results often obtained in the bacteriological examination of drinking water has been the basis for undertaking the following studies.

Bacillus coli communis, I believe, like B. typhosus, B. diphtheriæ, B. anthracis, etc., is a single microörganism, not a group; and if its biological and morphological features are sufficiently studied need not be confused with others. It is true that sometimes an atypical reaction is met with, but this irregularity, if carefully inquired into, will be found to depend, not upon the colon bacillus itself, but upon the condition in which it has been placed. The colon bacillus is commonly regarded as an acid-producing microörganism. The reaction, however, depends entirely upon the presence of sugar in the culture media; and in neutral bouillon the reaction of the culture will be alkaline.

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a. Production of indol. — This depends upon the presence of a proteid substance, peptone for instance. In such a medium, moreover, the presence of sugar inhibits the production of indol, which will be manifested only after the sugar has been exhausted by the colon bacillus. Further, under anaërobic conditions and by cultivating the organism upon special media containing phenol, nitrates, etc., the production of indol may be inhibited or completely abolished; and, following the ordinary technic, by using a one per cent peptone bouillon Lembke, Roux, Widal, Malvoz, Vallet, Dunham and others have reported cultures not producing indol, but otherwise typical of B. coli communis. Morris, however, by employing a five per cent peptone bouillon and making his tests after ten to twenty days, obtained positive indol reactions from the same cultures. It is due to such variations that our literature upon the organism in question is full of such classifications as "strong indol-producing colon bacilli," or marked "distinct," "weak," "faint" and finally "negative" indol-producing types. Such classifications are the result of too hasty conclusions from superficial observations, are presumed to depend upon variations in the organism when in reality they are the result of variations in the medium of cultivation and the technic employed.

Much to my surprise I have often observed a positive indol reaction in sterile meat sugar-free bouillon; and a close study of the subject has convinced me that the practice of preparatory fermentation of the meat juice with bacillus coli, as recommended by Smith and followed by leading bacteriologists abroad and in this country and described in all text-books, cannot be too strongly condemned. This preliminary fermentation with the colon bacillus for eighteen to twenty-four hours (and by neglect often forty-eight or more hours) is sufficiently protracted for the production of more or less indol, which then remains in the medium. The sterilization I found to be quite without effect in this reaction, as the medium thus fermented gave typical reactions before and after exposure not only of thirty minutes to 100° C., but also after exposure for half an hour to twenty or thirty pounds steam pressure. To this doubtless is due our new literature on "indol-positive typhoid cultures." In the State Department of Health Laboratory, in the Pathological Laboratory of the University of Pennsylvania, I employ a strong saccharolytic organism, isolated from water, producing 80–100 per cent of gas in eighteen to twenty-four hours, rapidly exhausting all sugars and not producing indol in the most careful test. With the medium thus prepared I have never obtained the slightest trace of indol in any typical cultures which I have examined; and it is my belief that no true typhoid organisms can produce indol, and that no true B. coli communis ever fails to show the reaction of Salkowsky.

b. Non-liquefaction of gelatine. — Almost every bacteriologist is of the opinion that a liquefying organism does not belong to the colon group, and that the bacillus coli never liquefies gelatine. It is not the question of liquefaction or no liquefaction which I wish to discuss, but rather the conditions under which such an important reaction is tested. The procedure recommended by the American Medical Association includes incubation at 20–22° C. and the use of medium of 1–1.5 per cent acidity, both of which I have found unsatisfactory, not because Bacillus coli will be affected by the reaction of 1.5 per cent acidity, but because the proteolytic fermentation proceeds better and more quickly in alkaline or neutral medium and takes place best at 37° C. As a routine procedure in the laboratory, I use neutral gelatine and incubate at 37° C. for from forty-eight hours to four days. The tube is then placed in ice water to harden the gelatine and examined for liquefaction or non-liquefaction of the medium. The method has given far better results, and what is of most importance it is the only way to eliminate gelatine-liquefying growths which at 20–22° C. in the acid gelatine do not produce proteolysis and are often mistaken for bacillus coli communis.

The classification of cholera spirilla into species, causing rapid, slow, slight and very slight liquefaction, I believe to be only a matter of the reaction of the medium and temperature of incubation. In case of a number of laboratory cultures as well as six others isolated from the Schuylkill river, tested after growth in neutral gelatine at 37° C. for forty-eight hours to four days, the liquefaction was complete; but was only partial when the organisms were kept under other cultural conditions.

c. Amount of gas. — It is regarded as characteristic of Bacillus coli that there should be produced a 50–75 per cent volume of gas in the closed arm of the fermentation tube in twenty-four to forty-eight hours (of which the relation of hydrogen to carbon dioxide is represented by the formula $H : CO_2 : : 2 : 1$) also that the fermentation is usually completed in twenty-four hours at 37° C. I have observed, however, cultures of Bacillus coli recently isolated from water producing no gas at all in twenty-four hours and only fifteen per cent or less after forty-eight hours at 37° C. The relation of hydrogen to carbon dioxide just mentioned may be regarded as correct, but it is by no means constant and reliable, a formula $H : CO_2 : : 3 : 2$ being even more frequently obtained, and formulas such as 3 : 1 or 4 : 1 or even higher may be observed according to the time at which examination is made. If cultures are closely observed it will be noticed that after twenty-four hours, when the gas formation is stopped, a gradual reabsorption of the CO_2 by the medium takes place, and the result gives an apparent excess of hydrogen. Further, when NaOH solution is added to absorb the CO_2 a partial vacuum is produced and should the mouth of the fermentation tube be imperfectly closed by the thumb or by a rubber stopper, access of air is permitted and the results may fail to show any carbon dioxide at all. It is possible, therefore, from conditions in which the culture is placed or from failure in the technic, to obtain a typical colon bacillus gas formation from an organism which under more careful observation would show the contrary.

The above points are presented in order to point out that the irregularities obtained in cultures are not due to different types of Bacillus coli, but to the conditions under which the culture is grown, or to imperfect technic, and to indicate that the organism should be regarded as essentially a monomorphic microbe.

With this view in mind, an attempt was made to find some reactions to serve as constant and reliable means of differentiation. After a series of tests it was found that if, in testing a number of tubes, .25 cubic centimeter of a forty-eight-hour culture of various organisms on dextrose bouillon was rapidly boiled in about five cubic centimeters of a ten per cent solution of NaOH, there will appear immediately after boiling a clear yellowish lemon color in the tubes of Bacillus coli; while in others, as an indication of the absence of Bacillus coli, the solution will remain clear and colorless, taking on a slight pinkish color after five to ten minutes; this reaction I have arbitrarily called "Test 1."

In another and independent observation conducted in other cultures isolated from water, I found that if about one cubic centimeter of a ten per cent solution of NaOH and then one cubic centimeter of a fifty per cent solution of H_2SO_4 be added to the cultures, some tubes will remain colorless while others will take on a purplish coloration either at once or within a few minutes. Closer study of this reaction showed this to be positive as soon as a growth was apparent in the medium, even as early as four or five hours incubation at 37° C. in neutral bouillon; and further investigation indicated that this purple coloration with NaOH and H_2SO_4 was characteristic of the Bacillus coli cultures. This reaction I have arbitrarily called "Test 2."

This last test shows the color reaction upon the addition of acid and its disappearance when alkali is added in excess; this is a direct reverse of the color reaction of Test 1, the color of which is discharged by acid and reserved by alkali. The color of Test 2 is not produced in the presence of sugar. It is apparently related to the presence of indol or some indigo derivative. Test 1 depends upon the biological action of the bacteria upon the sugar while Test 2 depends upon the action of Bacillus coli communis upon proteid substance; and the very striking and ready production of these color reactions serves materially in facilitating the differentiation of Bacillus coli. Further study is in progress to determine the nature of these reactions.

Action of the colon bacillus in sugar. — It was deemed desirable to avoid experimenting in this connection with the different kinds of sugars, as lactose, saccharose, fructose, mannite, etc., since while such study undeniably is of scientific interest, the multiplication of these sugar-media opens the chance of too ready and disastrous confusion of results; based on the fact that any saccharolytic microorganisms having the power of splitting other sugars have in my work never failed to attack dextrose, my observations were made upon cultures in media containing this sugar alone. Bacillus coli was incubated in a five per cent dextrose bouillon, and the culture daily examined polariscopically for the exhaustion of the sugar in the medium. It was found that the sugar after forty-eight hours remained the same as after twenty-four hours; in other words, that Bacillus coli showed but a weak sugar-splitting power, the saccharolytic action ceasing after twenty-four and sometimes after eighteen hours. With this fact in view, established by identical results in a number of experiments on the same line, it was thought well to make the same observations with other cultures which also possess saccharolytic activity, but which gave atypical reactions for Bacillus coli communis. From a number of such strains in the laboratory one was selected and incubated in five per cent dextrose bouillon and daily polariscopic examination pursued as in case of the true colon bacillus above mentioned. In this instance the sugar was found to be considerably diminished after eighteen to twenty-four hours, and to have entirely disappeared from the medium in from two to three days at 37° C. The results in tabular form were as follows:

Control sterile dextrose bouillon	1.17 per cent.
Bacillus coli culture after 24 hours at 37° C.	1.01 "
" " " " 48 " " 37° C.	1.01 "
" " " " 72 " " 37° C.	1.01 "
Allied species " " 24 " " 37° C.	0.66 "
" " " " 48 " " 37° C.	0.18 "
" " " " 72 " " 37° C.	0.00 "

These results, indicating the more complete saccharolytic ability of this allied species than that of Bacillus coli communis, indicate a constant feature of the various species in the group of microörganisms liable to be confused with Bacillus coli, another reliable differential test. In order to avoid the necessity for polariscopic examination of the cultures a series of investigations was pursued in which Fehling's solution was employed. The cultures as before were tested after twenty-four, forty-eight, and seventy-two hours incubation at 37° C., the copper sulphate solution diluted with equal parts of water as usually done in qualitative determinations of urine for sugar, and divided among a number of small test-tubes, one cubic centimeter being placed in each. To these the culture was added in increasing amounts, beginning with one, two, three, etc., drops up to one cubic centimeter, and the mixture then boiled. The result was very striking. The controls or non-inoculated medium gave positive sugar reactions with one or two drops according to the percentage quantity of sugar in the material; cultures of Bacillus coli gave positive reactions with about twice the amount added as in case of the controls, two to three drops; while the allied species failed to show reduction of the copper even after the addition of as much as one cubic centimeter of the culture. Often tests were conducted with different proportions of dextrose in the medium, from .1 per cent to five per cent dextrose bouillon and after forty-eight hours incubation at 37° C. the differentiation was the most typical. These findings have been confirmed in routine examination of a great number of cultures obtained from water and other sources during the past four years during my connection with the Filtration Bureau and later with the Pennsylvania Department of Health, cultures answering fairly to the characteristics of Bacillus coli showing exhaustion of the sugar only in a few cases, which on further investigation prove to be impure.

In view of such results I have tentatively proposed for that group of organisms which present characteristics similar to that of Bacillus coli but not corresponding completely to this organism, and which are commonly spoken of collectively as the "Colon Group," the substitution of the name "the saccharolytic group," based upon their splitting action in dextrose. The leading features of this saccharolytic group may be said to consist in their powerful action on dextrose, their usual failure to produce indol, and their tendency to cause liquefaction of gelatine. In the group, however, are a few individual types which fail to liquefy gelatine and a few which will produce indol. The separation of such examples may, however, be definitely made by the colorless to pinkish color reaction of Test 1,,or by the absence of the purple even reaction of Test 2, as above described, and by the test of their exhaustion of sugar from a one per cent dextrose bouillon medium after incubation for forty-eight hours at 37° C. This last reaction arbitrarily called "Test 3."

Being convinced of the importance of this strong sugar reaction of the saccharolytic group and its absence in the case of Bacillus coli, an investigation was made to determine the explanation of the difference manifested. Two suppositions were considered: first, that Bacillus coli may possess a slower action upon the sugar; or second, that it produces some substance which inhibits the saccharolysis which would otherwise proceed as in the saccharolytic group. Both types of organism begin to form gas at about the same time, but the colon bacillus produces gas more slowly than the group of allied species and its gas production ceases after twenty-four to forty-eight hours. The saccharolytic group, on the contrary, after beginning to produce gas, about the same time as Bacillus coli, continue more rapidly and do not cease until the sugar is entirely exhausted, the duration varying with the percentage quantity of sugar in the medium. At the same time it was found that the acidity of the medium was greater with Bacillus coli, which produced from three to five per cent in forty-eight hours; while the saccharolytic group produced only one to three per cent in the same period. This difference suggested that the greater acidity of the medium in case of Bacillus coli may exert an inhibitive influence upon the further action of the organisms upon the sugar. By adding a few grains of sterile calcium carbonate to the cultures after the fermentation had stopped and absorption had begun, with the effect of neutralizing the media, it was found in confirmation of this supposition that more gas is evolved and the sugar further diminished (even to exhaustion). As suggested by Dr. Smith the acidity of the culture was found to be due to the presence of lactic acid.

Before concluding I would like to point out briefly that, in view of the apparent variations of Bacillus coli, Booker recognizes seven varieties of organisms of the colon group resembling Bacillus coli morphologically and biologically (but with no especial mention of the production of indol); that Gilbert describes five types (*a*, non-motile but otherwise typical Bacillus coli; *b*, non-productive of indol, but otherwise typical Bacillus coli; *c*, non-fermenting lactose, but otherwise typical Bacillus coli; *d*, non-motile and non-fermenting lactose, but otherwise typical Bacillus coli; *e*, non-motile non-fermenting lactose, non-production of indol, but otherwise typical Bacillus coli); that Fremlin regarded fermentation of dextrose and coagulation of milk as the most reliable indication of Bacillus coli; that others regard the fermentation of dextrose alone as sufficient evidence of the identity of Bacillus coli. It is remarkable to note the elasticity of Bacillus coli as disguised at present under the name of "the colon group." I have observed bacteriologists in responsible positions to identify as Bacillus coli cultures of organisms which for no other reason than the appearance of pink colonies on litmus lactose agar, the coagulation of milk, and the production of an atypical reaction of indol were taken as such; and on further examination I have found some of these cultures to be made up of some variety of cocci or other bacteria not related to B. coli. As a matter of fact if we accept all the variations which have been enumerated for Bacillus coli, we are bound to admit almost all bacteria into the group; and it is with the hope of more sharply defining the characteristics of the true colon bacillus, and at the same time of indicating important features of the allied species, that the two colon tests and the matter of a difference in saccharolytic forms above outlined are presented.

From the above, I believe the following conclusions to be logical:

1st, That the saccharolytic group as its name implies represents not merely one, but different kinds of microörganisms commonly found in nature, especially in water, characterized by its predominating action in splitting dextrose.

2d, That the constant occurrence of this group in water may prove to be a factor in itself which may shed a new light on our vital problems of the bacteriology of water.

3d, That Bacillus coli must not be confounded with the colon group, which I name "Saccharolytic group," and that the saccharolytic group should have no relation to Bacillus coli.

4th, That since the saccharolytic group is shown to be more related to what at present is regarded as the colon group, the substitution of "Saccharolytic" instead of colon group is more comprehensible, and I hope will assist in doing away with the confusion which the colon group presents, and will especially aid in placing Bacillus coli as a distinct type of microörganism and not an indefinite chain of them, as is the condition at present.

5th, That Bacillus coli in addition to the recognized characteristics will be positive to Test No. 2 and negative to Tests No. 1 and No. 3 (that is, it will fail to exhaust the sugar in one per cent dextrose at 37° C. in forty-eight hours); while contrary to this the "Saccharolytic group" may in many ways present characteristics of Bacillus coli, but will always be negative to Test No. 2 and positive to Test No. 1 or Test No. 3 (that is, it will exhaust the sugar in forty-eight hours at 37° C. in one per cent dextrose broth).

6th, B. coli should be discarded as an agent for exhausting the sugar in the meat juice and one of the Saccharolytic group used instead.

[In conclusion I desire to extend my appreciation and most sincere thanks to Dr. Samuel G. Dixon, Commissioner of Health of the State of Pennsylvania, for his valuable criticisms on this paper; to Dr. Allen J. Smith, Professor of Pathology, and Dr. John Marshall, Professor of Chemistry at theUniversity of Pennsylvania for their personal interest and valuable suggestions, and to Dr. Herbert Fox, Chief of the Laboratories, for his valuable assistance during the progress of this work.]

EXPERIMENTAL OBSERVATIONS UPON THE VALUE OF INTESTINAL ANTISEPTICS.*

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The value of antiseptic drugs has long been a subject of dispute. Some observers, especially the French, following Bouchard, have claimed much for such remedies. Other clinicians appear to have very little faith in their efficiency. In the discussion upon Intestinal Autointoxication at the Wiesbaden Congress in 1898, the general opinion was expressed by Professor Mueller and others that it is hopeless to expect to disinfect the intestinal canal by drugs, and that there are no intestinal antiseptics worthy of the name. In one of the last works upon the subject Herter says that he has come to the conclusion that as a class antiseptic drugs do very little good in effecting a diminution of the putrefactive anaërobes of the intestines. In answer to these opinions it may be said that antiseptic drugs have never been investigated in a thoroughly scientific manner, and perhaps it would be better to reserve our judgment until their action has been tested more thoroughly. If it can be proven that intestinal antiseptics, as a class, influence the growth of the intestinal bacteria, and especially if it can be shown in what manner they do this, then a definite place of more or less importance will be found for them in the therapy of gastro-intestinal disease.

One difficulty in determining their true value clinically lies in the fact that they are seldom given a comparative trial, but are used in connection with drainage of the bowel and stomach and regulation of the diet. Consequently, the action of the drugs is obscured and ground is given for skepticism as to their value because, of course, diet and drainage will usually do the work without the aid of drugs. The experimental observation upon their action has been

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inconclusive because no very comprehensive work has been done upon the subject, and the various observations that have been made have been somewhat contradictory.

It has been difficult to find a satisfactory index by which we can measure directly the effect of a drug upon the intestinal bacteria. The chief methods that have been employed have been as follows:

First. Bouchard used the toxicity of the urine and feces as an index of the amount of autointoxication. This has some advantages, and at the same time certain disadvantages, one of which is that it is very hard to argue from the effect of a poison upon the smaller lower animals what its effect will be upon the human being.

Second. The aromatic bodies in the urine have long been used as an index of the amount of absorption of products of intestinal putrefaction, and secondarily of the activity of the intestinal bacteria. It is now the opinion of those qualified to judge that the method is not reliable, either as an indication of the amount of intestinal putrefaction or of the absorption of bacteria products, especially it is incorrect as an indication of the action of antiseptics. In support of these statements I can do no better than quote from two of the latest authoritative writers upon the subject:

> In Osler's Modern Medicine (i, 275), Alonzo Taylor says: "Since we are not able at the present time to estimate or control the amount of aromatic derivatives eliminated in other forms than paired with the sulphuric acid it is obvious not only that the estimation of indican must often be of no value, but also that the estimation of the conjugated sulphates must often yield an uninterpretable result, and one that will permit of no inference as to the degree of intestinal putrefaction."
>
> Herter says in "Bacterial Infections of the Gastro-intestinal Tract," 1907: "One difficulty in measuring the action of many of the antiseptic substances which have been used depends on the fact that they either decompose with the liberation of aromatic substances capable of pairing with sulphuric acid and forming ethereal sulphates, or they themselves are aromatic bodies capable of pairing in this manner. A study of the indican is not open to this objection, but there are cases of intestinal decomposition in which the ethereal sulphates may be considerably above the normal, although little or no indican is excreted."

There are several methods of directly observing the effect of drugs upon the intestinal bacteria:

(1.) The living bacteria may be counted by plating a known quantity of feces in agar. A large number of bacteria that are present in the small bowel and upper colon die before they are passed in the feces, and consequently such observations must be made by obtaining the feces from a fistula at the lower end of the ileum. This has the advantage that it shows the effect of the antiseptic directly upon the microörganisms at the point of their greatest activity, but the disadvantage that simple plating in one culture medium will not detect all the bacteria in the feces, especially the anaërobic varieties. Moreover, only a small portion of the matter is examined, and the feces are far from being homogeneous. The necessity of a fecal fistula, too, limits the field of investigation, especially in the human being.

Schuetz observed the action of various drugs by passing certain easily recognized saprophytic bacteria through the bowel, and noting the number of them that passed through alive during the administration of the different antiseptics.

The method of Strasburger measures the whole amount of bacteria in the stool, dead as well as living. I have employed this procedure during the past winter in some one hundred stools, and believe that, while it is not a perfect means of separating the bacteria from the feces, it is far in advance of any other method of estimating intestinal bacterial activity as a whole. The process has elements of technical error, but they are small, and if the results are considered in a comparative manner, and are regarded to some extent in round numbers, then I believe that the estimation of bacteria by weight is a good index of general bacterial activity in the intestine, and of the action of the various remedies used to influence the bacteria. I have modified the method in one particular in order to secure greater homogeneity of the stools before a portion is taken for examination.

Strasburger's method has the disadvantage that it does not distinguish between putrefactive and fermentative bacteria. However, it can be ascertained by a study of the stool derived from a test diet whether the digestion of starch or meat is at fault and, consequently, which form of bacterial action is favored. When the method is used as an index of the action of intestinal antiseptics in normal persons with good digestion, it is very difficult to determine whether putrefactive or fermentative bacteria are most affected. For the present we must be content with an idea of the action of such drugs upon the bacteria as a whole; and for this purpose I believe that Strasburger's method is in advance over any used heretofore.

An ideal intestinal antiseptic should have the following properties:

First. It should not be toxic if absorbed.

Second. It must be easily diffusible through the intestinal contents.

Third. If intended for the intestine it must not be destroyed by the gastric secretion or must be given in a covering that is resistant to hydrochloric acid.

Fourth. It must not be too irritating to the intestinal mucous membrane.

As I have said, the results of previous investigations into the effect of these intestinal antiseptics have been somewhat conflicting. The drugs have been used in different ways and with different methods of measuring their effect upon the intestinal bacteria. Sometimes the bacterial growth seems to be diminished, in other observations the bacteria seems to be increased by the action of the drugs.

It will be seen, from reference to the following summary, how conflicting these different observations have been:

Stern found that bacteria gradually died out in some calomel stools which were allowed to stand for several days. In other calomel stools this did not take place.

Von Mieczkowski found that menthol and tannopen given by the mouth diminished the number of colonies in specimens of feces taken from a fistula at the lower end of the ileum; while with itrol and bismuth the results were negative.

Schuetz introduced a culture of Vibrio Metschnikoff into a duodenal fistula, and observed the number of these bacteria recovered alive in the stools. Castor-oil did not influence the microörganisms. Calomel in large doses increased the number that came through alive.

Schönenborn used Strasburger's method as an index. He found that naphthalene (two grams daily), itrol (.3 gram daily), thymol (1.5 grams daily) increased the bacteria, and that salicylic acid mixed with the food diminished them.

Hoffman found that isoform given by the mouth diminished the number of colonies in the feces obtained from an iliac fistula.

Bouchard found that naphthalene, iodoform, and charcoal diminished the toxicity of the urine and stools.

Herter says that salicylates given as aspirin or salol have in his experience exerted some action in diminishing the output of indican.

My own observations have been undertaken in order to attempt to answer the fundamental question upon which all investigations of intestinal antiseptics must rest; namely, whether it is possible to influence bacterial growth in the intestine of normal subjects by antiseptic drugs given through the mouth. To do this I have used Strasburger's method as an index. Subjects upon which the experiment is made should be normal because in them it is possible to exclude the variations in the amount of bacteria that may take place during the experiment due to the deceased condition and not to the drug. No systematic work of this sort as far as I know has ever been done. The two antiseptics employed were chosen because they fairly represent two important classes of such remedies, and both are known to possess decided antiseptic power.

Bismuth salicylate is non-irritating, and is one of the drugs that depend upon salicylic acid for its activity, which substance has been generally regarded as one of the best preparations for disinfection of the gastro-intestinal tract. Beta-naphthol, on the other hand, belongs to the more irritating and toxic class of such remedies.

The subjects that I chose for my observations were, with one exception, without intestinal symptoms, or any signs of intestinal disease.

The drugs were from reliable manufacturers and were given in capsuls. Every effort was made, and I believe with success, to keep the subjects under the same physical conditions in all the stages of the experiments.

The diet employed in three of the cases was that known as full hospital diet, in which the three main constituents are fairly well balanced, and there is certainly no excess of meat. One of the other cases was upon a full home diet, also well balanced, and the last case was upon the so-called soft diet of the hospital.

The amount of bacteria passed varies from day to day with the amount of the stool and other factors. Consequently, all of my comparisons have been made by obtaining daily averages of the stools for three or four days.

First a control observation was made for several days without drugs, and then the result of this was compared with the daily average of a similar period after the drug had been given for several days. The results were quite conclusive and may be summarized as follows:

(1.) In the three cases in which bismuth salicylate was used the daily average amount of bacteria fell within three days after the drug was given to one-half or one-quarter of what it was in the control observation.

(2.) In two cases in which beta-naphthol was given, the bacteria fell after three days to about one-half of the control.

(3.) In the third beta-naphthol case the bacteria increased for three days and then remained about the same as the control for three days. This was the only patient in which there were gastro-intestinal symptoms. She was a young woman with gastroptosis and insufficient gastric secretion, but with no decided symptoms of intestinal disturbance. In this case it is not clear why the drug failed to act.

It indicates, however, that we must not assume without further investigation that the action of these drugs will be the same in a diseased bowel as in a healthy one.

It seems highly probable that the normal intestine has some power of self-protection against the development of certain pernicious forms of microörganisms, and probably also against excessive bacterial growth in general. This property may lie in the intestinal wall as suggested by Schuetz, who introduced saprophytic bacteria through a duodenal fistula and found that a large proportion of them were killed in their passage through the bowel. As the intestinal contents did not affect the growth of these bacteria in vitro, he concluded that the bactericidal power probably lay in the intestinal wall, and was biological in character. Other observers, notably Herter, have suggested that the colon bacilli, which are normal inhabitants of the bowel, exert some antagonism to the excessive growth of certain pernicious microörganisms in the intestinal contents. Wherever this power of self-protection lies, it apparently exists and seems to be dependent for its activity upon the preservation of the normal intestinal functions. Anything which interferes with the normal function of the bowel will impair this power of self-protection, and an increase of bacteria above the normal will result.

Thus I have found that an excessive amount of HCl in the gastric secretion increased the amount of bacteria in the feces (Journal American Medical Association, Aug. 14, 1907), although HCl is really an antiseptic. However, when it passes into the bowel in unduly large amounts it probably acts as a chemical irritant, disturbs the normal intestinal function, and impairs its power of self-protection against bacteria.

While antiseptic drugs have the power to check bacterial growth under some circumstances, under others they seem to have no effect, and sometimes they even increase bacterial activity. So it may well be that irritating antiseptic drugs will act differently in intestines in which the functions of the mucous membrane are disturbed than they will act under normal conditions. The failure of the beta-naphthol to reduce bacterial growth in the case of indigestion may be an instance of this. That is, the intestinal mucous membrane was more easily irritated than in the healthy subjects, and its self-protective power was impaired; consequently, the beta-naphthol did more harm to the intestinal mucous membrane than to the bacteria; and hence bacterial activity was increased.

I may summarize my results as follows: I found that bacterial growth in the intestine was decidedly diminished in normal subjects during the administration by the mouth of two typical intestinal antiseptics, and I think that this is evidence in support of the belief that it is possible to check bacterial activity in the intestine by antiseptic drugs.

The whole subject needs much more thorough investigation, which I hope to give it in the future. At the present time it seems highly probable that, as a rule, the so-called intestinal antiseptics do more harm than good in diseased states of the gastro-intestinal tract. Still the fact remains that under normal conditions such drugs have a very powerful effect in diminishing bacterial activity in the intestine as measured by the total bacteria of the feces, and it may be possible that there are some conditions of disease in which their action will be of benefit.

In conclusion I wish to say that I am firmly of the opinion that evacuation of the intestinal contents, combined with regulation of the diet, are by far the most efficient means at our command to check excessive bacterial activity in the intestines.

In my observations upon the amount of intestinal bacteria I have been impressed again and again by the important part that diet plays in influencing bacterial growth. I have made no comparative study of the effects of different foods, but I have no doubt from what I have seen in my work that by regulating the amount and character of the food ingested we have the strongest and surest means of checking excessive bacterial activity in the intestines.

TABLE I.

Bismuth salicylate.

I. Control observation without drugs.

Cases	I. Healthy Male Adult.	II. Male Adult.	III. Female Adult.
	Full home diet.	Heart disease; no intestinal symptoms; full hospital diet.	Paralysis of arm; full hospital diet.
Daily average	4 days.	3 days.	3 days.
Amount feces	251.0 cc.	161.6 cc.	210.0 cc.
Dried weight feces	41.1 g.	23.6 g.	15.0 g.
Dried weight bacteria	7.44 g.	4.99 g.	2.74 g.
Per cent bacteria	18.1	21.1	18.2
Bismuth salicylate	2.4 grams 40.0 grains daily—in doses of 5 grs. every 2 hours.		

II. Observation begun after stools were black.

Daily average	3 days.	4 days.	3 days.
Amount feces	233.0 cc.	86.2 cc.	135.0 cc.
Dried weight feces	39.3 g.	13.7 g.	12.4 g.
Dried weight bacteria	3.26 g.	1.15 g.	1.17 g.
Per cent bacteria	7.14	8.3	9.4
Ratio of reduction	2⅓ : 1	4⅓ : 1	2⅓ : 1

III. Control observation after bismuth had disappeared from stools.

Daily average	3 days. Stools free for 3 days.	2 days. Stools free for 6 days.	
Amount feces	247.0 cc.	150.0 cc	
Dried weight feces	49.3 g.	12.27 g.	
Dried weight bacteria	10.05 g.	2.51 g.	
Per cent bacteria	22.21	20.4	

TABLE II.

Beta-naphthol.

I. Control observation without drugs.

Cases	IV. Female Adult.	II. Male Adult.	V. Female Adult.
	Semi-liquid hospital diet; no intestinal symptoms.	Full hospital diet; heart disease; no intestinal symptoms.	Gastric neurosis; middle grade acidity; medium hospital diet; no intestinal symptoms.
Daily average	3 days.	2 days.	3 days.
Amount feces	133.0 cc.	150.0 cc.	140.0 cc.
Dried weight feces	14.4 g.	12.2 g.	13.64 g.
Dried weight bacteria	2.23 g.	2.51 g.	1.69 g.
Per cent bacteria	15.6	20.4	12.4

II. Beta-naphthol { 1.8 grams / 15 grains } daily.

Daily average	4 days. Begun 3d day.	4 days. Begun 2d day.	3 days. Begun 3d day.
Amount feces	62.5 cc.	96.2 cc.	93.3 cc.
Dried weight feces	8.5 g.	11.7 g.	17.5 g.
Dried weight bacteria	0.9 g.	1.44 g.	3.51 g.
Per cent bacteria	10.0	12.3	20.0
Ratio of reduction	2.4 : 1	1.7 : 1	1 : 2

Second observation.

Daily average	3 days. Begun 6th day; 20 grs. daily.	....	3 days. Begun 8th day.
Amount feces	73.3 cc.	....	106.0 cc.
Dried weight feces	10.6 g.	....	9.02 g.
Dried weight bacteria	0.97 g.	....	1.73 g.
Per cent bacteria	9.1	....	19.1
Ratio of reduction	2.2 : 1	....	1 : 1 +

THE TECHNIC OF THE METHOD OF ESTIMATING BACTERIA BY WEIGHT.

The possibility of separating the bacteria from the rest of the feces depends upon the fact that the bacteria are so nearly of the same specific gravity as distilled water that they cannot be centrifugalized out of a watery suspension of the feces, but remain suspended in the supernatant fluid. Taking advantage of this fact the bacteria can be removed by washing with the centrifuge. Then, if the specific gravity of the wash water is lowered by the addition of large amounts of alcohol, the relation of the bacteria to the fluid is changed to such an extent that the microorganisms can be readily centrifugalized, separated, dried, and weighed.

Unless the period of passage of the feces has been ascertained to be normal, it is better to mark the beginning and end of each period of examination by carmine. The use of the Schmidt diet is not necessary. Indeed, I have found that this diet is not desirable because it leaves very little residue and so of itself reduces the total amount of bacteria to a lower point than that which is usually found.

The whole stool is saved. Unless the feces are liquid they are rubbed up with a known amount of distilled water until they are smooth and semiliquid and as homogeneous as it is possible to make them. This is a modification of my own intended to make it easier to obtain a specimen of the stool that is fairly indicative of the average amount of bacteria contained in each cubic centimeter. Strasburger takes but two cubic centimeters of the formed feces. It seems to me that since the different portions of the stool differ so in consistency and composition this method of Strasburger leads to considerable error. I believe that my modification insures a much more accurate idea of the average consistency of the stool.

Two portions of five cubic centimeters are measured off with a pipette of large caliber. I use for this purpose an ordinary five cubic centimeter pipette with the tapering end cut off and with the necessary correction made at the upper mark. One of these portions of five cubic centimeters is put into a porcelain dish and dried upon a water bath and later in a drying oven in order to determine the dried weight. The addition of a little alcohol and thorough mixing will hasten the process of drying and prevent caking of the feces. The second portion is washed free from bacteria. This is done as follows: The wash water is a one-half per cent solution of hydrochloric acid in distilled water. The acid increases the solubility of the salts and soaps of the feces. I usually employ about one hundred cubic centimeters of this solution at the beginning of the washing. The feces are thoroughly mixed with the wash solution and then are centrifugalized. The use of the water motor or electric centrifuge is almost essential. Each tube is centrifugalized for about one and a half minutes, then the cloudy supernatant liquid is poured through a layer of gauze. This fluid contains the bacteria in suspension. All of the mixture (the wash water and the feces) is centrifugalized in the same way and then the residue in the tubes is shaken up with more of the wash water and centrifugalized again This is repeated until the supernated liquid after centrifugalizing is quite transparent, showing that approximately all the bacteria have been washed out. If a smear is made of the residue at this point it will be found that the bacteria are not entirely washed away but are evidently very much reduced. They occur singly, while in the unwashed feces they are in great lumps and masses. I do not believe that it is practicable or even possible to wash the feces entirely free from microörganisms.

Strasburger recommends that the wash water be recentrifugalized for a short time at high speed in order to remove any stray particles of solid residue from the suspension of bacteria. I believe this is a mistake, for if the decanting is carefully done in the first instance, then in my experience the sediment obtained with the second centrifugalization is composed almost wholly of bacteria which would be lost if this part of the procedure was always carried out. The suspension of bacteria is then mixed with a liberal portion of alcohol and evaporated down slowly at a temperature of 40° to 50° C. until it amounts to not more than fifty cubic centimeters in all. This takes approximately twenty-four hours. It is then mixed with at least twice its volume of alcohol, preferably absolute alcohol, although this is not absolutely necessary. This lowers the specific gravity of the fluid to such an extent that now the bacteria readily centrifugalize out. The mixture is then centrifugalized until the supernatant liquid is quite clear. This may take thirty minutes or more for each tube. The residue which consists of the bacteria is washed with pure alcohol and is shaken up with ether to remove the fat; then it is washed again with alcohol. All of this washing is done by means of the centrifuge. The bacteria are next washed out of the tube with a little alcohol and evaporated to dryness and dried in the oven at moderate heat, dried in the desiccator and weighed. Smears of the final preparation show that it consists of bacteria with a few very minute particles of other material. These particles are only visible with high power and are very few in number, perhaps two to each field of one-twelfth inch lens. They stain with methylene blue, and Strasburger suggests that they are cellulose, which they may well be. At any rate, the error arising from the inclusion of these small particles in the dried weight of the bacteria must be very small and is probably balanced by the bacteria that it is not possible to wash out of the residue in the first washing. During the preparation of the bacteria the first portion of five cubic centimeters has been dried and weighed. We then know the dried weight of five cubic centimeters, the weight of the dried bacteria in five cubic centimeters, the original volume of the stool and the volume after the addition of a known amount of water. It is then easy to calculate the data that we desire, namely, the volume of the stool, its dried weight, the weight of the dried bacteria, and the percentage of bacteria in the dried weight.

REFERENCES.

Bouchard. "Lecons sur les Auto-intoxications dans les Maladies." Paris.

Adolph Hartman. Mittheilungen aus den Grenzgebieten der Medicin und Chirurgie, xv, 605.

Herter. "Bacterial infections of the digestive tract." New York, 1907. 330.

Mieczkowski. Mittheilungen, aus den Grenzgebieten der Medicin und Chirurgie, ix, 1902, 405.

Fr. Mueller. Verhandlung des Congr. für innere Medicine zur Wiesbaden, 1898.

Schönenborn. Inaug. Diss. Bonn, 1903; Verhalten der Bakterien in Stuhl bei Eingabe von Antiseptics.

R. Schuetz. Archiv. für Verdauungs Krank., 1901, 58.

Stern. Verhandlung des. Congr. für innere Medicine, 1898; Zeitschrift für Hygiene, xii, 1892.

Strasburger. Zeitschrift für Klin. Med., xlvi, 1902, Hft. 5 and 6; xlviii, 1903, Hft. 5 and 6; also "Fæces des Menchen," 2d ed., Berlin, 1905, IV., abschnitt.

Alonzo Taylor. Osler's Modern Medicine, i, 275.

A STUDY OF PHAGOCYTOSIS IN DIPHTHERIA.*

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This study was undertaken to determine: (1) the action of human phagocytic cells towards the diphtheria bacillus as we meet with this organism in the various stages of diphtheria uninfluenced by serum therapy; (2) to continue the study of this activity towards the Klebs Loeffler bacillus in the same patient after treatment by diphtheria antitoxin had been begun; (3) to note the activity toward the pneumococcus and streptococcus by phagocytic cells from the same patient under the same conditions; (4) to note whether or not our present dosage of diphtheria antitoxin, given with the usual interval between doses, promotes maximum phagocytic activity towards each of these organisms; and (5) if change in phagocytic activity be found under serum treatment to determine its cause.

From a clinical standpoint we had in mind a study to learn if maximum resistance toward the diphtheria bacillus could be maintained and at the same time maintain or, better, increase resistance towards the often dangerous associated pneumococcus or streptococcus. All clinicians know that in mixed diphtheria infection the associated organism is a serious problem from the standpoint of treatment. Pathologists constantly see pneumococcus and streptococcus lesions at autopsy on those dead of diphtheria, and bacteriologists commonly find these organisms in culture from the various viscera of these cadavers. The diphtheria toxin can readily be rendered harmless with serum. We know, however, that we cannot at present render harmless the streptococcus and pneumococcus toxins.

With these principles in mind, observations were made with the blood of fifteen cases having acute diphtheria before serum treatment was given; with these fifteen patients at

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frequent intervals after serum had been given until convalescence was established; of one case of acute tonsilitis not bacteriologically diphtheria; of two healthy children who had diphtheria seven years and one year previously; of eight children who were healthy and had not had diphtheria; of four normal children before and after the injection of serum; of two cases of chronic diphtheritic otitis media before and after injection of diphtheria antitoxin; and of one chronic case of diphtheritic otitis media before and after the injection of diphtheria toxin.

Our study embraces three hundred and sixty-four observations on phagocytosis with virulent diphtheria bacilli, one hundred and fifty-nine observations on phagocytosis with streptococci of varying virulence, ninety-five observations on phagocytosis with non-virulent pneumococci, one hundred and twenty-four leucocyte counts, one hundred and twenty-five differential leucocyte counts, and a series of special laboratory experiments.

Observations with the diphtheria bacillus were made in fifteen cases before beginning serum treatment with the following results: One patient the first day of disease showed twelve per cent of his phagocytes active; two second-day cases showed eighteen and twenty-three per cent active respectively, an average of 20.5 per cent; four third-day cases showed sixty-one, forty-eight, thirty-five, and fifty-eight per cent active respectively, an average of 50 5 per cent; six fourth-day cases showed forty-six, forty-nine, thirty-four, nine, twenty, and ten per cent respectively, an average of twenty-eight per cent; one fifth-day case showed five per cent, and one seventh-day case showed twenty-nine per cent. The average number of active phagocytes in the fifteen acute cases of diphtheria before giving serum was 30.46 per cent.

Further observations with these cases were made at the following intervals after giving serum:

Three cases one hour after serum injection, one case one and one-half hours after; one case two hours after; one case two and a half hours after; three cases three hours after; two cases four hours after; three cases five hours after; sixteen cases six hours after, and every succeeding twelfth hour until convalescence was well established. It was found that the most marked changes took place in the first hour when there was an average rise to 56.96 per cent in the percentage of phagocytic cells, or 26.5 per cent above the zero line. This standard or zero line was obtained by taking the average percentage of phagocytic white cells before antitoxin was administered in the fifteen cases and was found to be 30.46 per cent, as already stated. The least change occurred in the third hour when there was a rise of one per cent. These changes are shown on composite chart No. 2.

The average percentage of phagocytic cells toward the diphtheria bacilli in the fifteen cases varied from twenty to forty for the first fifteen days after the administration of antitoxin. Two cases observed until the sixteenth and seventeenth days showed a percentage of forty-five and fifty-one respectively. There was only one case noted on each of these days (see composite chart No. 3).

In the first six hours eight cases showed an increase and seven a decrease in phagocytic activity after the administration of antitoxin, but the average increase was greater than the average decrease as 34.5 per cent is to twenty-five per cent. The eight cases showing an increase had an average number of sick days of 14.7, with one death on the fourth day with bronchopneumonia. The seven cases showing a decrease had an average number of sick days of 18.6 per cent and no deaths. The average increase was 11.5 per cent and the average decrease 13.1 per cent, showing a total decrease of 1.6 per cent for the entire number of observations in acute diphtheria, viz., three hundred and forty-three.

Blood drawn from the ear, finger, and toes showed practically no variation in the number of leucocytes and none in the percentage of cells phagocytic. It was intended to study blood drawn from the tonsils, but all the later cases were such small children that coöperation could not be secured.

In order that we might know definitely whether phagocytic activity was relatively or absolutely increased, we determined to note changes in leucocytosis in a series of cases taking the blood at the same time and from the same site as for phagocytic study. It was also decided to make differential leucocyte counts at the same time to learn if leucocytic increase was noted in all types of leucocytes or only in phagocytic cells.

In ten of the fifteen cases leucocyte counts were made before and after antitoxin was administered. Five showed a fall, four a rise, and one remained stationary. Of the four showing a rise, two occurred one and one-half hours after, one three hours after, and one four hours after giving antitoxin. The greatest rise occurred at the fourth hour (four thousand five hundred); the least rise occurred at one and one-half hours (seven hundred); the greatest fall occurred at the fourth hour (seven thousand four hundred and fifty); the least fall occurred at the third hour (two thousand two hundred and fifty.) (See composite leucocyte chart.)

In ten cases differential counts were made, four hundred cells being counted. In eight of them the curve of the polymorphonuclear cells corresponded to the curve of the phagocytic cells. In the other two cases the curves were decidedly at variance.

In all the cases from one to 1.3 per cent of normoblasts and myelocytes were found, and the transitional cell count ran from one to three per cent.

Two kinds of antitoxin were used, one prepared under the supervision of the Board of Health of this city, the other commercial concentrated by the Gibson method. There was no difference in their action on the phagocytes.

The ages of the fifteen cases ranged from nine months to twenty-seven years, and seemed to have no effect on the phagocytes.

Race showed no influence.

Of the fifteen cases, eight were males and seven females. Six of the females showed a rise in the percentage of phagocytic cells and one a decrease after the administration of antitoxin. Of the eight males, two showed an increase and six a decrease after diphtheria antitoxin was injected.

The height of the fever, severity of the attack, and day of disease showed no effect on the phagocytic index in the cases studied after serum was injected.

About half of the cases showed a rise and half a fall in phagocytic activity between night and morning. These observations were continued throughout the twenty-four hours at intervals of six and twelve hours.

In order to determine what would occur in normal individuals the blood of ten healthy children taken at random was studied and showed the following phagocytic activity toward the diphtheria bacillus:

Case.	Age.	% Phag.	Previous Infectious Disease.
1*.....	14	14	Measles. The history of this case is questionable.
2......	11½	2	"
3......	8	6	No infectious disease.
4......	12	16	Diphtheria five years ago.
5......	12	5	Typhoid fever.
6	8	19	Diphtheria one year ago.
7......	8	0	None.
8......	7	2	"
9......	9	1	"
10......	9	0	Tonsilitis.

* No culture was taken, hence we cannot exclude the possibility of this boy being a diphtheria bacillus carrier.

Blood removed from several of us and several hospital attendants not having had diphtheria showed practically no phagocytic activity toward the diphtheria bacillus.

One patient, Case C, coming under observation the fifth day of illness with an acute sore throat, had on admission an exudate covering a portion of each tonsil and a patch of similar character on the middle of the dorsum of the tongue. Cultures made from these sites on three successive days showed no diphtheria bacilli.

On admission her phagocytes showed no desire to take up diphtheria bacilli. One hour after injecting five thousand units of antitoxin, fifty-three per cent of her phagocytes were active and at subsequent intervals of six hours, twelve hours, and eighteen hours, thirty-six, thirty-three and 22.5 per cent were active respectively. Phagocytosis toward the Klebs Loeffler bacillus continued for four days, declining gradually to almost the starting point.

A correspondingly rapid increase in phagocytic activity toward the streptococcus was seen in the patient after serum was given; the decline following more rapidly with a gradual increase from the thirty-sixth hour until the observations were discontinued on the tenth day of illness.

Effect of diphtheria antitoxin on phagocytosis with streptococcus and pneumococcus.

One hundred and fifty-nine observations were made with streptococci and ninety-five with pneumococci. There was no marked variation in the number of cocci taken up by the phagocytic cells nor in the number of cells phagocytic before and after the injection of antitoxin.

Effects of antitoxin on chronic infections of the middle ear with Klebs Loeffler bacilli known to be fatal to guinea-pigs.

Two children with "chronic" positive cultures were each injected with two thousand five hundred units of diphtheria antitoxin and the effect noted on phagocytosis. Six observations were made in each case with diphtheria bacilli, streptococci, and pneumococci. The phagocytic index was noted immediately before the injection, one hour after injection, and then every three hours. The first case showed a very slight decrease (three per cent), followed by a slight increase (five per cent), in the percentage of cells phagocytic to diphtheria. There was a fall of two per cent, followed by an increase of two per cent and a fall of two per cent, in the activity of phagocytes toward pneumococci; with the streptococcus there was a rise of six per cent followed by a fall of four per cent and a rise of two per cent.

The second case showed no change whatever to either of these organisms.

CONCLUSIONS.

The blood of normal individuals shows practically no phagocytosis towards the diphtheria bacillus.

The blood of patients ill with acute diphtheria drawn from finger, ear, or toe shows an active phagocytosis towards this organism.

Phagocytosis appears to reach its maximum about the fourth day of diphtheria in those untreated with serum.

Diphtheria antitoxin has no constant effect on phagocytosis or leucocytosis.

Phagocytosis toward the diphtheria bacillus shows no particular variation in patients of differing ages or races.

Diphtheria antitoxin has no effect on the activity of phagocytes toward streptococci or pneumococci.

If we grant that phagocytes are barriers preventing bacterial invasion, then it would appear that injection of large amounts of antitoxin does not lessen one's susceptibility to streptococcus or pneumococcus infection.

We report the following laboratory experiments:

Experiment 1. — Four children, none of whom had ever had diphtheria or antitoxin, were chosen to note the effect on phagocytosis toward diphtheria bacilli after the injection, in Case 1, of five cubic centimeters sterile horse serum; Case 2, of five cubic centimeters of horse serum plus five per cent trikresol; Case 3, with five cubic centimeters plain horse serum concentrated by methods used in refining diphtheria antitoxin, and Case 4 with two thousand five hundred units of antitoxin concentrated by Gibson's method.

All four cases showed a rise in phagocytic activity. The percentage of phagocytic cells rose six per cent in four hours in each of the cases injected with plain serum. During the next two hours, Case 1 fell two per cent, and Case 2 rose two per cent; in the following two hours Case 1 rose seven per cent, and Case 2 fell five per cent. In the first four hours there was a rise of three per cent in Case 3, and of two and one-half per cent in Case 4. In the following two hours each rose ten per cent, and the last two hours Case 3 fell two per cent, and Case 4 fell four per cent.

Effect on leucocytosis in these four cases was as follows: In the first four hours Case 1 showed a rise of one thousand six hundred per centimeter; Case 2 showed a fall of four hundred, Case 3 a rise ,of five thousand, and Case 4 a rise of one thousand twelve hundred. In the succeeding two hours, Case 1 showed a fall of two thousand per millimeter, Case 2 a fall of four hundred, and Case 3 a fall of four thousand. Case 4 showed a rise of two hundred. In the following two hours Case 1 showed a fall of two hundred; Case 2 showed a rise of three thousand, Case 3 showed a fall of four hundred, and Case 4 showed a fall of five hundred.

In Case 1 there was a fall of one million six hundred thousand in the red cell count; the other three cases did not vary far from normal, the count ranging from four million to five million three hundred thousand.

Three of the cases showed a fall in eosinophiles after injection, while Case 1 showed a slight rise after the injection.

Experiment 2. — This work was suggested and carried out by one of us (Mr. Weston) in a case of infection of the ear by diphtheria bacilli where reinjection by serum failed to increase phagocytosis.

Such remarkable results have been achieved with vaccine therapy that it seemed to warrant our giving it a trial in this infection. Workers with vaccine have been treating conditions brought about by organisms producing an endotoxin. But this particular case was an infection due to an organism elaborating an exotoxin. The reaction on the part of the body after an injection of vaccine results in the formation of an antitoxin and a cytolysin, but before sufficient antitoxin can be generated to neutralize the toxin injected opsonins are increased with an increased phagocytosis. So far as we know it has not been shown which had the greater effect on opsonin production, the organisms or their toxins, or whether both were necessary.

It was decided then to find by experiment in the case of diphtheria infection of the ear which was more active, toxin or bodies of bacilli. For this purpose a series of cases were to be treated with an injection of pure toxin, a second series with bodies of dead bacilli, and a third with bacilli plus toxin. The experiments were carried no further than the injection of pure toxin in one case. Lack of time and material brought the work abruptly to a close. We therefore report this case with the other laboratory experiments, and only as an experiment.

Case R. — A. S., female, aged one and one-third years. Enteric fever six months ago, Children's Hospital, severe attack, great emaciation, nasal diphtheria during early convalescence. Admitted to the Municipal Hospital 3–22–07, sixth day of nasal diphtheria, serum treatment before admission, otitis media present on admission. Discharged on negative cultures 4–4–07, greatly emaciated and weak, ear had ceased discharging. Re-admitted 4–10–07, ear discharging freely and showing many Klebs Loeffler bacilli, given two thousand five hundred units diphtheria antitoxin and repeated in thirty-day intervals for several months. Diphtheria organisms were constantly found in the ear discharge, cultures tested repeatedly on guinea-pigs proved virulent. The patient had lived in the hospital for a period of five and a half months and attempts had been made to increase her phagocytosis towards diphtheria organisms by serum injection. This case is referred to earlier in this paper as one of two chronic cases of diphtheritic otitis media, treated without success. June 29, 1907, two thousand five hundred units of B. of H. antitoxin had been given with no effect on phagocytic activity.

Two months after this injection (9–1–07) at the time of this experiment, the diphtheria bacilli from her ear were of such virulence that five cubic centimeters of a forty-eight-hour-old alkaline bouillon culture was fatal to a two hundred and sixty gram guinea-pig in seventy-one hours. Toxin made of these organisms was of such strength that .05 cubic centimeter was fatal to a guinea-pig two hundred and fifty grams in weight in seventy hours. Wright states that the best results were obtained if the vaccine were injected in such a place that the lymph drained through the affected area before reaching the general circulation. In this particular case it was impossible to inject at such a site. Five millionths (.000005) cubic centimeter of toxin was injected under the skin over the right shoulder. This toxin was made from the bacilli isolated from the child's ear. The bacilli used in the work on phagocytosis were from the same source.

The following changes were noted. In one hour there was a rise in the percentage of white cells phagocytic from sixteen to twenty-five, this was followed by a steady fall lasting six hours, when in two hours it rose to thirty per cent. The next twelve hours brought the percentage down to one and in twelve more hours it rose to thirty-seven per cent. For the four succeeding days it gradually declined until it reached the starting point, ten per cent (see chart No. 35, case R).

White cells. — After the seventeenth hour the neutrophilic granules failed to stain but by the end of the fourth day they stained normally. At the seventeenth hour the nuclei of the leucocytes showed signs of disintegration. In twenty-three hours the nuclei stained poorly, and in twenty-nine hours the nuclei showed the greatest amount of disintegration. At the fortieth hour the disintegration was less and by the fourth day had entirely disappeared.

Red cells. — Ten hours after injection the red cells showed signs of disintegration which cleared up on the fifth day.

In each of these observations a control test was made with Mr. Weston's blood using the same solutions ana suspensions. In seventeen days the diphtheria bacilli disappeared from the ear and the patient was discharged.

TECHNIC USED THROUGHOUT THE WORK.

Organisms. — The K. L. bacillus in this work was of such virulence that the injection of .5 cubic centimeter of a forty-eight-hour-old alkaline bouillon culture was fatal to a two hundred and seventy-five gram guinea-pig in seventy hours. In cases A and D and K, both the bacilli from the patient's own tonsils and those from the stock cultures were used. There was no variation in the phagocytosis. Only the regular stock culture was used in all other cases. This stock culture was obtained from the tonsils of a child suffering with diphtheria.

The streptococci used were isolated from the tonsils of a child suffering with diphtheria and were at all times fatal to mice.

The organisms were grown on Loeffler's blood serum mixture and subcultures were made on glycerine agar every forty-eight hours.

The pneumococci were isolated from the pharynx of a child infected with diphtheria. They were non-virulent when used in these experiments. Non-virulent organisms were used because the phagocytes refused to take up virulent ones; the phagocytic index toward virulent pneumococci being zero.

Preparing the bacterial emulsions. — Ten or fifteen cubic centimeters of sterile normal saline solution were poured into a culture tube containing a forty-eight-hour-old culture of the organisms on glycerine agar. The resulting emulsion was placed in another tube, centrifugalized and the supernatant fluid, very faintly tinted by the water of condensation, was poured off. Sterile saline was again added, the emulsion well agitated and centrifugalized till the supernatant fluid was found to show the proper density. We found the emulsion corresponding with McFarland's scale No. 5 gave the best results. The comparison of densities was made with McFarland's Nephelometer.

Collecting the blood, measuring, mixing, etc. — A pipette with one end drawn out to a tube of fine bore about fifteen centimeters long and fitted with a rubber teat at the expanded end was used to collect the blood and mix the fluids. The expanded end was blocked with cotton and a mark about two-fifths centimeter from the other end was made. The part of the body from which the blood was drawn was cleansed with alcohol and pricked. A sterile solution of 1.5 per cent sodium citrate in normal saline solution was drawn up to the mark on the fine tube. A short column of air followed and the blood was drawn up to the mark. The two fluids were blown into a small tube, thoroughly mixed and carried to the laboratory a distance of two hundred yards.

A mark was made on a vaccine tube about 1.5 centimeters from the end. The citrated blood was drawn up to this mark followed by an equal volume of emulsion, a short column of air separating the fluids. The two were thoroughly mixed in a watch crystal, aspirated into a vaccine tube, which was then sealed at both ends and incubated twenty minutes. At the end of this time the fluid was blown on a cover-glass, mixed and a smear made with another glass. These were permitted to dry in the air and were stained by Marino's stain. Jenner's and Wright's stains are also satisfactory.

Counting. — The two cover-slips were counted on the same slide. Clark counted one and Weston the other. A comparison of the counts by the two workers showed practically no difference in results. Each one counted the first fifty leucocytes seen, passing by those in clumps.

In counting the diphtheria slide it was impossible to enumerate the individual bacilli in a cell because of their granules, so only the number of phagocytic cells was noted. With the cocci, however, the individual organisms were counted as was also the number of cells. The phagocytic index was obtained by dividing the number of cells counted (one hundred) by the number of cocci contained in the phagocytes.

In making the leucocyte counts care was exercised to obtain a free flow of blood without squeezing the part. The technic used was that everywhere employed in blood work and need not be detailed. The blood was counted at times when physiological increase in leucocytosis should have shown little influence on the cell count. Feeding hours for those having light house or soft diet, for meals, 6.45 A.M., 11.30 A.M., and 4.30 P.M., with a glass of milk at 10 A.M., 2 P.M., and 6 P.M. Hours for blood collection when six-hour counts were made were 4 and 10 A.M., 4 and 10 P.M., and either 4 A.M. and 4 P.M. or 10 A.M. or 10 P.M. in cases counted each twelfth hour. When single counts were made collection hours were 10 A.M. and 4 P.M.

The object in using the above technic was to approach as nearly as possible the body conditions and so make it possible to observe with a fair degree of accuracy the changes taking place in phagocytosis at any given time in the body of human beings.

[In conclusion we express our thanks to Dr. Joseph S. Neff, Director, Department of Public Health and Charities, and Dr. A. C. Abbott, Chief of the Bureau of Health, through whom it was made possible to undertake this work by appointing two of us, Messrs. Weston and Clark

Special Laboratory Assistants Municipal Hospital: Drs. Fife and Sykes, of the Philadelphia General Hospital for coöperation and supply of some material; Dr. Joseph McFarland for valuable suggestions, Dr. E. Burvill-Holmes for isolating a number of the organisms used; Dr. A. H. Stewart for preparing whole horse serum; Mr. T. J. Lynch and Dr. Bell for supplying us with refined concentrated antitoxin and for concentrating and refining whole horse serum, and Dr. A. B. Hitchens for supplying us with diphtheria toxin and some special glassware.]

Case A. — P. H., white, female, age nine months; admitted fourth day of illness. Pseudomembrane on both tonsils and nasal discharge suggests posterior nasal involvement; nose and throat cultures positive; impaired resonance over base of both lungs and harsh expiratory sounds found over same area. Death from bronchopneumonia twenty-six hours after admission; autopsy confirming diagnosis. Serum treatment, seven thousand five hundred units refined concentrated serum on admission; repeated in eighteen hours.

Case B. — R. B., white, male, age one and one-half years; admitted 5–30–07, fifth day of illness, pseudomembrane covering each tonsil, mucopurulent nasal discharge showing flocculi, marked laryngeal group with some stenosis; positive culture. Intubation in nineteen hours, tube worn three days. Serum treatment, ten thousand units refined serum repeated in twelve hours and again in twenty-four hours; a total of thirty thousand units being given. Recovery in twelve days without complication.

Case C. — A. T., white, female, one and one-half years of age; admitted 5–31–07, fifth day of illness; pseudomembrane anterior portion of each tonsil and over small area of the tongue in the mid-dorsal region. Three cultures negative, probably not diphtheria. Serum treatment, five thousand units B. of H. antitoxin on admission; not repeated. Rapid recovery; discharged eleventh day of illness.

N.B. — Chart of Case C of especial interest; one per cent of phagocytes active toward the diphtheria bacillus on admission. Great increase in activity after antitoxin. Other observations will be made in similar cases and in those in health, in order that the relation of serum injection to immunity may be better understood.

Case D. — Dr. J. D. W., white, male, age twenty-six years; admitted 6–9–07, second day of illness; entire tonsillar area, both tonsils covered with pseudomembrane and small patches seen on pharyngeal wall, positive culture. Serum treatment, seven thousand five hundred units concentrated serum on admission, repeated in seventeen hours and again in twenty-four hours; total, twenty-two thousand five hundred units. Uneventful recovery, discharged twenty-first day.

Case E. — Dr. G. F. C., white, male, age twenty-seven years; admitted 6–20–07, first day of disease; small area one centimeter of typical pseudomembrane on right tonsil, culture positive. Serum treatment, two thousand five hundred units concentrated serum on admission, not repeated. Uneventful recovery, discharged fourteenth day.

Case F. — M. A., white, female, age three years; admitted 6–29–07, fourth day of illness, pseudomembrane covered tonsils extending to lateral walls of pharynx, culture positive. Serum, five thousand units concentrated serum, repeated in twenty-two hours; total, ten thousand units. Uneventful recovery, discharged twenty-fourth day without complication.

Case G. — A. L., white, female, age nine years; admitted 7–7–07, second day of illness: pseudomembrane on posterior half of right tonsil, culture positive. Serum treatment, five thousand units B. of H. antitoxin on admission, repeated in fourteen hours; total, ten thousand units. Uneventful recovery, discharged fifteenth day in splendid condition.

Case H. — W. M., colored, male, aged ten years; admitted 7–8–07, seventh day of illness; pseudomembrane on both tonsils and pharyngeal wall, nares excoriated, bleeding from tonsils. Culture positive. Serum treatment, ten thousand units refined serum on admission, repeated in eighteen hours, again second and third days, and five thousand given fourth day after admission; total, fifty-five thousand units. Tedious recovery with myocarditis and slight paralysis, discharged in fair condition fifty-sixth day of disease.

Case I. — S. S., white, female, aged six years, admitted 7–12–07, third day of illness, pseudomembrane completely filling both nostrils with patches on skin surface of upper lip, both tonsils, anterior pillars and half arches covered, foul fetid breath, nose and throat cultures positive. Serum treatment, ten thousand units refined serum on admission, repeated twice in twenty-four-hour intervals; total, thirty thousand units. Good recovery, nose cultures positive long time, discharged fifty-sixth day in good condition.

Case J. — H. C., white, female, aged seven years; admitted 7–15–07, second day of illness, pseudomembrane covering greater part of both tonsils, culture positive; serum treatment, five thousand units refined serum on admission, repeated twice; total, fifteen thousand units. Rapid recovery, discharged thirteenth day of disease in good condition.

Case K. — T. C., male, colored, age eight years; admitted 7–16–07, third day of disease; pseudomembrane covering entire surface of large tonsils and extending to anterior half arches, culture positive. Serum treatment, five thousand units B. of H. serum on admission, repeated twice; total, fifteen thousand units. Rapid recovery; discharged fourteenth day of illness.

Case L. — M. A., white, female, ten years of age; admitted 7–18–07, fourth day of illness, pseudomembrane covering tonsils, anterior pillars, half arches, and uvula, positive culture. Serum treatment, ten thousand units refined serum on admission, repeated in eleven hours again on following day, and five thousand units given third day after admission; total, thirty-five thousand units. Good recovery in thirty-seven days.

N.B. — Case M, after several observations, was dropped because of learning of serum administration before we received her.

Case N. — H. G., white, male, three and one-half years of age; admitted 7–31–07, fourth day of illness, pseudomembrane entirely covering tonsils and filling nostrils, considerable swelling cervical lymph glands. Nose and throat culture positive. Serum treatment, seven thousand five hundred units B. of H. serum on admission, repeated in eighteen hours and on succeeding day; total, twenty-two thousand five hundred units. Good recovery, discharged twenty-ninth day of illness.

Case O. — G. R., white, male, age nine years; admitted 8–4–07, fourth day of illness; pseudomembrane covering greater portion of each tonsil, culture positive. Serum treatment, five thousand units B. of H. serum on admission, not repeated. Rapid recovery, discharged thirteenth day of disease.

Case P. — P. R., white, male, age six years; admitted 8–4–07, fourth day of illness; pseudomembrane covered both tonsils, culture positive. Serum treatment, five thousand units B. of H. serum on admission, not repeated. Rapid recovery, discharged thirteenth day of disease.

Case Q. — V. H., white, female, age four years; admitted 8–5–07, fourth day of illness; pseudomembrane covering greater portion of tonsils and half arches and plugging both nostrils. Nose and throat cultures positive. Serum treatment, seven thousand five hundred units refined serum on admission, same dose refined serum repeated next day and twenty-four hours later, seven thousand five hundred units B. of H. antitoxin; total, twenty-two thousand five hundred units. Good recovery, discharged sixteenth day of disease.

DESCRIPTION OF CHARTS.

COMPOSITE CHART NO. 1.

Black line indicates percentage of phagocytic white cells toward Diphtheria bacilli on the day of disease shown at the head of the column before the administration of antitoxin was begun. The black dots indicate individual cases.

COMPOSITE CHART NO. 2.

Black line indicates average per cent increase or decrease of phagocytic white cells toward Diphtheria bacilli after the administration of antitoxin. The time elapsing after serum injection is indicated at the head of the column. The black dots indicate individual cases. The zero line is obtained by taking the average number of phagocytic white cells in sixteen cases before the administration of antitoxin. It was found to be 30.46 per cent.

COMPOSITE CHART NO. 3.

The solid black line indicates the average percentage of phagocytic white cells toward Diphtheria bacilli on each day of disease. This includes observations made before and after serum administration.

COMPOSITE LEUCOCYTE CHART.

The solid line indicates the average leucocyte count in diphtheria. One hundred three successive counts were made. The counts made before and after serum administration are included.

Two second-day cases before serum administration averaged 20,200 leucocytes per cubic millimeter.

Two third-day cases before serum administration averaged 14,500 leucocytes per cubic millimeter.

Five fourth-day cases before serum administration averaged 20,169 leucocytes per cubic millimeter.

One seventh-day case before serum administration averaged 19,600 leucocytes per cubic millimeter.

COMPOSITE DIFFERENTIAL LEUCOCYTE CHART.

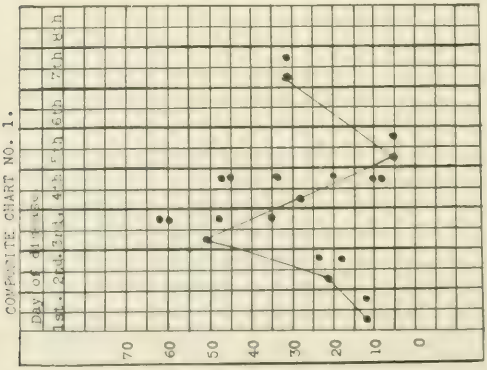
The above charts embrace the average result of 102 successive differential leucocyte counts made on different days of the disease, counts made before and after serum included, as follows:

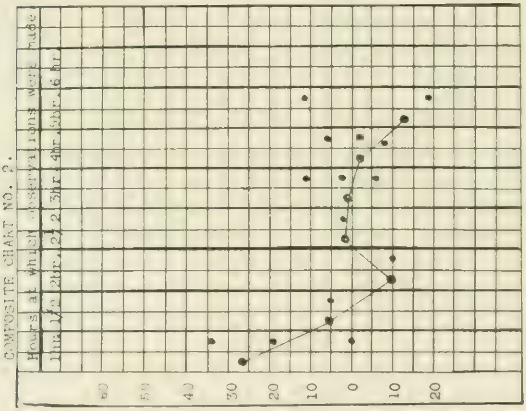
Second day, 2 cases, 3 counts.
Third day, 4 cases, 8 counts.
Fourth day, 9 cases, 15 counts.
Fifth day, 9 cases, 10 counts.
Sixth day, 9 cases, 9 counts.
Seventh day, 8 cases, 9 counts.
Eighth day, 8 cases, 10 counts.
Ninth day, 8 cases, 9 counts.
Tenth day, 8 cases, 8 counts.

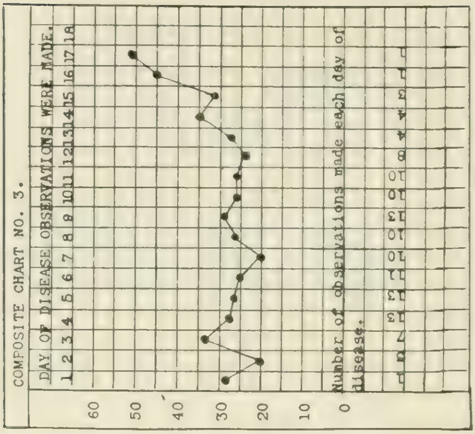
Eleventh day, 6 cases, 6 counts.
Twelfth day, 6 cases, 6 counts.
Thirteenth day, 3 cases, 3 counts.
Fourteenth day, 3 cases, 3 counts.
Fifteenth day, 2 cases, 2 counts.
Sixteenth day, 1 case, 1 count.

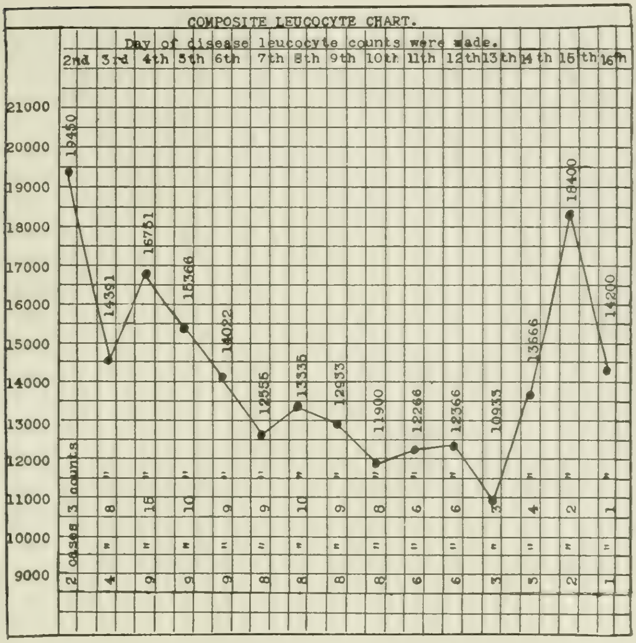
CHART NO. 35, CASE R.

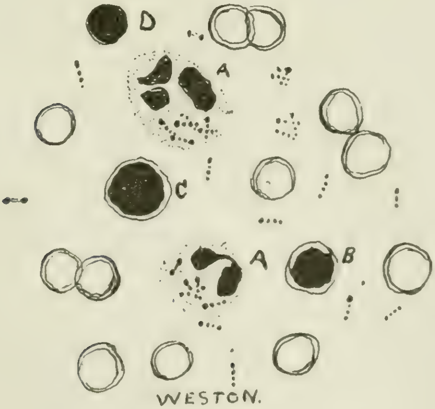
This chart shows changes occurring in the number of blood cells and alterations in phagocytic activity following injection of a toxin produced from a culture of the patient's particular strain of Diphtheria bacilli.


COMPOSITE CHART NO. 1.
Day of disease
1st. 2nd. 3rd. 4th 5th 6th 7th 8th
70
60
50
40
30
20
10
0


COMPOSITE CHART NO. 2.
Hours at which observations were made
1hr. 1/2 2hr. 2 1/2 3hr. 4hr. 5hr. 6 hr.
60
50
40
30
20
10
0
10
20


COMPOSITE CHART NO. 3.
DAY OF DISEASE OBSERVATIONS WERE MADE.
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
60
50
40
30
20
10
0
Number of observations made each day of disease.





A. Polymorphonuclear neutrophile containing diphtheria bacilli.
B. Normoblasts.
C. Large lymphocytes.
D. Small lymphocytes.

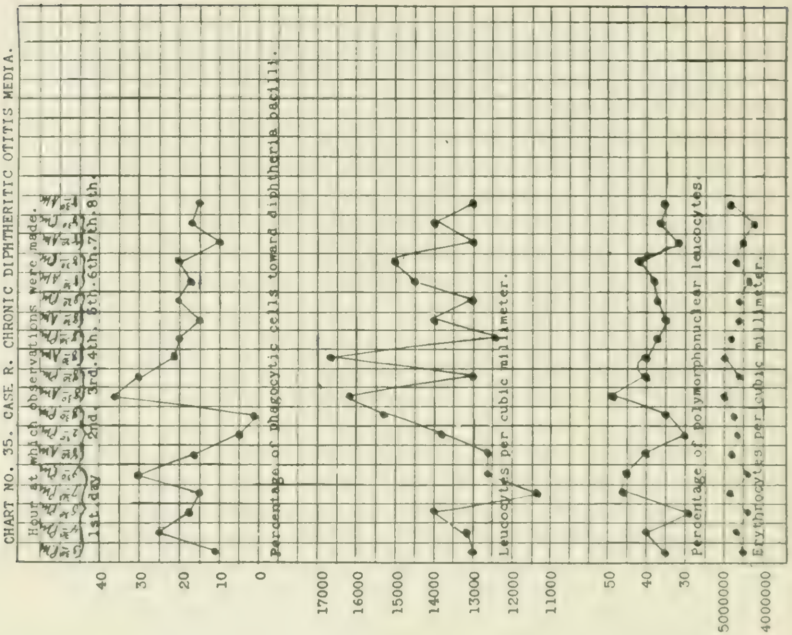
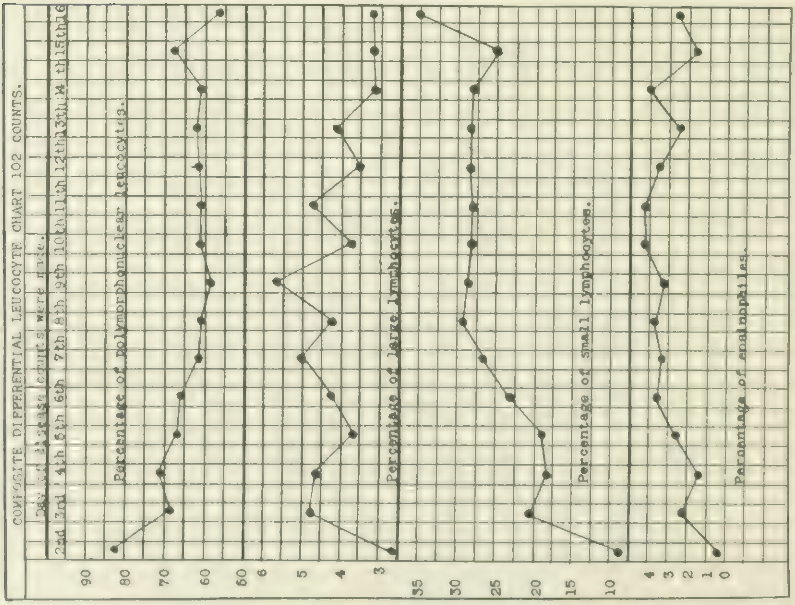


CHART NO. 35. CASE R. CHRONIC DIPHTHERITIC OTITIS MEDIA.



COMPOSITE DIFFERENTIAL LEUCOCYTE CHART 102 COUNTS.

SYRINGOMYELIA WITH SYRINGOBULBIA.*

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While syringobulbia is by no means rare, the following case presents a number of interesting features. These consist, clinically, of the presence of paralysis of the superior oblique muscle of the right eye, transient ptosis on one side, contracted fields of vision, hemiatrophy of the tongue, hemiplegia, and ataxia; and pathologically, the presence of cavity in one anterior pyramid of the medulla oblongata, with ascending degeneration in the anterior pyramid on the same side, the presence of intense lepto-meningitis, the predominance of the cavity on one side, and the probable syphilitic nature of the lesion of the spinal cord and meninges. Furthermore, the pathological findings have an important bearing upon the explanation of the bulbar symptoms in cases of syringomyelia and syringobulbia which are not due to the cavity formation.

The patient, a married woman fifty-nine years old, was admitted to the Philadelphia Home for Incurables Feb. 1, 1904.

F. H. — Her father died of phthisis, and her mother of heart disease. One brother was drowned, and one was killed. One sister died of asthma.

P. H. — There is no history of previous serious illness. She suffered from intermittent fever some years ago. She was married at the age of thirty-five years, never bore children, nor had any miscarriages.

In 1891 she began to stagger toward the left without vertigo. About the same time she frequently burned herself without recognizing it until afterward. She also had severe transient attacks of tic douloureux, associated with double vision.

Shortly after the onset of these symptoms, in December, 1891, she consulted Dr. John T. Carpenter, to whom she gave a history of having had headaches. I am indebted to Dr. Carpenter for the report of the examination of the eyes at this time. He stated that the entire nerve was altered in appearance, showing large globular hyalin masses, or so-called drusen

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tumors of the optic nerve. The nerve was grayer than it should be, but there was no contraction of the retinal vessels.

In November, 1892, she was again examined by Dr. Carpenter, who elicited a history of an attack of unconsciousness, occurring shortly before her visit to him, and also of intense pain in the branches of the left trifacial nerve, with fleeting double vision and unsteady gait.

In February, 1896 (five years after the onset of the disease), all the symptoms were more marked, and she could not walk without a cane. At this time there was considerable ataxia, and with her feet together and the eyes closed, she would have fallen if not supported. The knee jerks were increased.

On July 17, 1896, there were some sensory changes in the left arm, and sharp lancinating pains in the distribution of the cervical nerves added to the symptoms already described. There was at this time, also, a paresis of the superior oblique muscle.[1]

In August, 1896, she complained of numbness in the left arm and leg, and pain in the left arm. She also complained of a subjective sensation as of boiling water running down the bone in the left arm. The ataxia had increased, and the left arm and hand had begun to show signs of weakness.

The field of vision showed a peripheral concentric contraction for form and colors, more marked on the left side.

On July 21, 1902, all the symptoms had progressed markedly. The field of vision in the left eye was contracted almost to fixation point; in the right eye, to twelve inches. The field was mapped out as follows: temporal side, seven inches; up, seven inches; in, four inches; down, two inches. There was a deep pallor of the optic nerve.

When examined, shortly after her admission to the Home in February, 1904, she was found to be generally well preserved, excepting in the regions exhibiting local atrophy.

Atrophy. — The thenar and hypothenar eminences of the hands, especially on the left side, were markedly atrophied. The muscles of the forearm also appeared to be somewhat wasted on both sides, especially the flexors. There was apparently no wasting elsewhere in the upper or lower limbs. There was a marked right hemiatrophy of the tongue.

The station was very unsteady, and with the eyes closed the patient would have fallen to the ground if unsupported.

The gait was a curious one, being at the same time that of ataxia and of a left hemiplegia.

There was a marked ataxia in the arms, more apparent in the right than in the left, which, however, may have been due to the fact that the left arm was weak and somewhat spastic.

Reflexes. — The knee jerk on the right side was much increased; on the left side it could not be elicited on account of the rigidity present. The ankle jerk on the right was present, but on the left it could not be obtained on account of the spasticity. There was no clonus on either side. Babinski's reflex was readily developed on each side. The arm jerks could not be elicited on either side. The left arm and leg were distinctly rigid, while the right arm and leg were not at all spastic.

Sensation. — There was a subjective sensation of cold in the left hand, and of burning pain in the left forearm.

In the left hand there was almost complete loss of the thermal sense, and the pain sense was almost wholly lost over an area including the entire left arm, left anterior trunk to the median line, left side of the face, and the left anterior cervical region on both sides, extending only as far as the clavicle on the right, and posteriorly to about the tenth dorsal on the left, involving the entire scalp posteriorly.

There was loss of the thermal sense in the right hand, although this was not as pronounced as in the left hand.

From the elbow to the shoulder on the right side the patient confused heat and cold, and on the right side the thermal sense was lost as far down as the tenth dorsal spine.

Dr. W. C. Posey examined her eyes with the following result: The palpebral fissures were equal on both sides. There were no pathological lid signs present. Fixing in the median line caused slight rotary mystagmic movements, which became more marked at the limit of the excursion of the eyes in all directions. Tests showed a paralysis of the superior oblique muscle of the right eye. The pupils responded to light and in accommodation. There was simple atrophy of the optic nerve in both eyes, with persistence of the hyaloid changes already noted by Dr. Carpenter.

Examination of the eyes made in August, 1904, by Dr. Van Epps, showed the presence of cataractous changes in each lens. At this examination ptosis of the right upper lid was observed. Later, however, this symptom did not persist.

At the examination made in June, 1905, the paralysis of the left arm and leg had progressed so that she could not walk, and she was unable to use the left arm at all. At this examination the sensory disturbances had extended to the legs. The pain sense was lost in the right leg and thigh, but sensations for touch, heat, and cold were preserved. The temperature and pain senses were lost in the entire left leg.

There were marked flexor contractures of the left forearm muscles, so that the fingers of the hand were tightly flexed on the palm, and this contracture could not be overcome by the examiner. There was also some contraction of the forearm on the arm, and the left leg was spastic and totally paralyzed.

The atrophy of the hand muscles had progressed moderately.

The patient died in February, 1907.

At the autopsy the brain and spinal cord were removed and placed in formalin solution for two weeks, and afterwards in Müller's fluid.

The pia of the medulla oblongata and pons was much thickened, and the medulla oblongata was twisted out of shape. The change in the pia extended well over to the cerebellum on each side, the whole anterior surface in this region, including the basilar artery, presenting a matted appearance (see illustration). The basilar artery was closed by a thrombus which had undergone calcareous degeneration.

The brain showed a moderate degree of hydrocephalus, involving all the horns of the lateral ventricles, especially the posterior horns. The fissure of Sylvius was not dilated.

Sections from various levels of the cord and medulla were stained by the Weigert hematoxylin method, and with the hematoxylin, eosin, and thionin stains.

The spinal cord, from the end of the conus, to about the third lumbar segment, was divided into ten portions, as it was impossible to count the roots.

In sections from Block No. 2, from the lower part of the conus, there was a linear cavity in the left posterior horn, extending almost to the posterior periphery of the cord. The pia was thickened in this region, and infiltrated with round cells.

At Block No. 3, both lateral columns were degenerated, that on the left side more intensely. The cavity occupied the same position, but was a trifle larger.

At No. 4. the cavity became very slight, scarcely visible, and at No. 5 it was only visible under a high power.

At No. 7 the cavity extended into the anterior horn on the left side, which was partly destroyed. It expanded very much at this level, and invaded the posterior horn. The anterior roots on the left side were only slightly degenerated. There was slight degeneration of the posterior column on the left side.

At No. 8 the cavity occupied the same position, although the posterior horn was invaded slightly more than in the level below. The anterior and posterior roots, especially the latter, stained less deeply. The degeneration of the posterior white columns on the left side was more marked.

At No. 9 the cavity extended forward almost to the central canal, and backward to the posterior border of the posterior horn. At this level the anterior horn was intact. There was slight degeneration of the crossed pyramidal tract on each side, more intense on the side of the cavity. Degeneration of the left posterior column was still present.

At No. 10 the cavity was linear in shape, and extended almost to the central canal in front, and to the posterior border of the posterior horn behind. The degeneration in the crossed pyramidal tracts was very marked on both sides. The degeneration of the left posterior column still persisted.

At the third lumbar segment the anterior limb of the cavity extended toward the central canal.

At the second lumbar segment the cavity was smaller, the degeneration of the crossed pyramidal tracts was more intense, and the posterior column on the left side was still slightly degenerated.

At the eleventh thoracic segment the cord was much distorted. The cavity, which was linear in shape, extended toward the central gray matter on the right, and was less extensive in the posterior horn than in the segment below. The degeneration in the left crossed pyramidal column was intense, and more so than on the right side. The right direct pyramidal tract was also degenerated, and the degeneration was less marked in the posterior columns than in the second lumbar segment. The posterior roots showed traces of degeneration on the left side.

At the tenth thoracic segment the cavity involved the anterior horns slightly, and was more extensive in the posterior horn, the latter being almost entirely destroyed. It also invaded slightly the posterior columns on the left side. The degeneration in the crossed pyramidal tracts was still quite marked.

At the seventh thoracic segment the cavity destroyed the left anterior and posterior horns in large part, extended to the posterior border of the posterior horn. The pyramidal tract on the right was much degenerated, while the degeneration in the posterior column had disappeared.

In the fourth thoracic segment the anterior horn on the left side was destroyed in large part. The anterior portion of both posterior columns was involved, and the cavity extended forward into the lateral column on the left.

In the second thoracic segment the cavity was larger and involved the left anterior and posterior horns, and extended into the right posterior horn. The right direct pyramidal tract and both crossed pyramidal tracts were much degenerated. The roots stained fairly well.

At the eighth cervical segment the cavity occupied a large part of the right posterior horn, involving the intermediate gray matter of the right side extensively, and destroying the left anterior and posterior horns. The left crossed pyramidal tract was degenerated intensely; the right, slightly. Most of the fibers of the posterior columns were well preserved. There was degeneration of the border zone in both anterolateral columns, which was more intense on the right side. The leptomeningitis at this place was very intense, especially posteriorly.

At the sixth cervical segment the appearance was the same, excepting that the degenerating in the border zones was much more intense. In the ground fibers of the lateral columns there was an area of degeneration on the right side, situated in about the middle portion. The roots stained well.

The medulla oblongata at its lowest level was degenerated in large part. The cavity destroyed the nuclei of the posterior columns on the right side, and there was also a cavity present in the right pyramid. The leptomeningitis was intense, the pia being much thickened, and the blood vessels altered. The direct cerebellar tract was degenerated on the left side.

At the level above this the cavity was much smaller and was situated in the posterior portion of the medulla, occupying the position of the nuclei of the posterior columns on the right side. The cavity in the right pyramid was still present.

At a still higher level there was a large cavity which destroyed the nucleus of the right hypoglossus nerve, and extended forward and inward, lying in the position of the ninth and tenth nerve fibers, and reaching nearly to the periphery of the medulla oblongata, destroying the right olive, the fibers of the right twelfth nerve, the internal arcuate fibers of the same side, and causing degeneration of the lemniscus of the opposite side. There was also a small cavity in the right pyramid, slit-like in character. The external arcuate fibers on the left side were degenerated and the cerebellar olivary fibers on this side stained poorly.

At a still higher level the cavity was situated posterior to the olive, cutting the internal arciform fibers, and extending forward and inward, opening into the central canal. The cavity could still be seen in the right anterior pyramid.

The degeneration of the lemniscus on the opposite side was marked, and was more intense in the anterior half.

A little higher still, at the superior limit of the olive, the cavity had disappeared. There was at this level degeneration of the pyramid on the right side, and degeneration of the contralateral lemniscus. The nerve fibers of the ninth and tenth nerves were normal on both sides.

At the next level, at which the acoustic fibers made their exit from the medulla oblongata, the degeneration of the left lemniscus was still present. There was also a slight degeneration of the right pyramid, occupying the outer and posterior portions especially.

At the level of the sixth nucleus the degeneration of the left lemniscus was still visible. The nerve fibers of the facial nerve, and the nuclei of the sixth nerve, were intact. The degeneration of the right pyramid at this point had disappeared.

At the level of the fourth nucleus there was still partial degeneration of the left lemniscus, but it was much less than at the level below. The lateral fillets stained well. There was no degeneration in the pyramidal tracts, although the fibers on both sides of the raphe stained less intensely than the remainder of the pyramidal fibers. The decussation of the fourth nerve showed no degeneration. A small area of softening was present at this level, situated in the central portion of the pons, cutting the raphe.

The optic chiasm showed some degeneration, especially on the right side anteriorly. It was also present on the left side, but was not so extensive, and was situated centrally.

The right optic nerve was degenerated at the periphery, leaving healthy fibers in the middle. The left optic nerve was degenerated, but less so than the right.

The right third nerve showed no degeneration. In the left third nerve there was only one small bundle of degeneration observed, the nerve in large part being normal.

Both right and left fifth nerves were slightly degenerated.

The right seventh nerve contained a few degenerated fibers. The left seventh nerve was normal.

Both right and left eighth nerves were slightly degenerated.

The right ninth and tenth nerves stained very poorly, and contained but few unchanged fibers. The left ninth and tenth nerves were normal.

Sections from the lumbar region, stained by thionin, showed some, although not extensive, degeneration. Some of the nerve cells had lost their processes. In many there was much yellow pigment, and in one cell the yellow pigment almost filled the entire cell. In a few the nuclei were eccentric, though many were still centrally situated. The chromatic elements were granular, and arranged around the nucleus. Most of the cells were more or less swollen. There were, however, some normal cells present.

In the cervical region the pigment was granular in many of the cells, and in some there was distinct atrophy of the chromatic bodies. Some of the cells were very well preserved; others were distinctly swollen, staining poorly.

In sections from the paracentral region on both sides the perivascular spaces were distended. The pia was not diseased. A few of the nerve cells contained a large amount of yellow pigment, and in some the chromatic substance was atrophied.

The pia of the entire cord was the seat of a round-cell infiltration, and was much thickened. This inflammatory process extended up to the superior border of the pons, and became more intense at the second thoracic segment, increasing in intensity in an upward direction, so that the medulla, pons, and cerebellum were matted with the pia, and the medulla oblongata was twisted out of shape.

In the lumbar region numerous blood vessels with thickened walls were seen clumped together in the cavity and associated with round-cell infiltration. This was also seen in the cervical region, to a less degree. In one section the round-cell infiltration could be traced from the pia through the cord as far as the wall of the cavity.

The blood vessels of the pia, in the region of the cervical cord, medulla, and pons, were altered. In some the walls were thickened, the lumen narrowed, and there was also some perivascular round-cell infiltration.

Summary. — A woman fifty-nine years of age, developed, sixteen years before her death, typical symptoms of syringomyelia with bulbar involvement. There was left hemiplegia, ataxia of both arms and legs, and atrophy of the hand muscles and of the right half of the tongue. There were paralysis of the superior oblique of the right eyeball, transient slight ptosis of the right eyelid, and nystagmus. Characteristic sensory disturbances were observed.

A cavity was found in the spinal cord extending from the conus medullaris into the medulla oblongata to the superior limit of the olive, involving chiefly the left anterior and posterior horns of the cord, and from the second thoracic segment upward to the right posterior horn also.

In the medulla oblongata the cavity was on the right side, and destroyed the nucleus of the right twelfth nerve, the nuclei of the right posterior columns, the right olive in its lower levels, the right arcuate fibers, and the right anterior pyramid. The left ninth, and tenth nerves, the optic nerves, the left third, and both fifth and eighth nerves were more or less degenerated. Ascending degeneration of the left lemniscus and the right pyramid in the medulla oblongata, and degeneration of the direct and crossed pyramidal tracts and the left posterior column in the lower part of the cord were present. There was a leptomeningitis extending from the conus medullaris to the upper limit of the pons, and was most intense from the second thoracic region to its upper limit.

The clinical symptoms of this case which deserve special mention are the paralysis of the right superior oblique muscle of the eyeball; the nystagmus; the contraction of the visual fields; the ptosis of the right eyelid; the involvement of the fifth nerve; the ataxia; the predominance of the motor symptoms on the left side; the apoplectic onset, and hemiatrophy of the tongue.

The paralysis of the superior oblique muscle is perhaps unique. While Schlesinger has found paralysis of the external ocular muscles in syringomyelia mentioned thirty-three times in the literature, as occurring in thirty-one patients, no mention is made of palsy of the fourth nerve. Diplopia was present in eleven per cent of three hundred cases, but was probably due to involvement of the sixth nerve, the one usually attacked in syringomyelia.

Very rarely is affection of the oculomotor nerve observed; although ptosis, which, however, was transient in character in my case, has been described.

Nystagmus, which was present in my case, is a frequent symptom. The cause of this is not yet clear. Some authorities, according to Schlesinger, view nystagmus as an anomaly of the muscle tone, or as an asthenic symptom of the eye muscles. He quotes Landois, who stated that injury to the corpus restiformis in animals causes nystagmus, and also Hollopeau, in whose case the cavity reached as high as the corpus restiformis. In Schlesinger's case, with pronounced nystagmus, the corpus restiformis was injured. In my case the corpus restiformis was apparently normal. In three hundred and thirty cases in the literature studied by Schlesinger there were fifty-one examples of nystagmus and nystagmus-like movements.

Contraction of the visual fields, which was so marked in my case, was present in one hundred and thirty cases in the literature studied by Schlesinger. He believed that in the majority of cases of syringomyelia the visual field is normal. When the visual fields are contracted it is, in most instances, due to concomitant hysteria. There are, however, a few cases in which the visual fields — especially for colors — are contracted, and in which there is no hysteria present. My case belongs to the latter classification beyond a doubt, and was due to the atrophy of the optic nerve, which was present on both sides.

Involvement of the fifth nerve has been frequently described. Schlesinger, in two hundred cases in the literature, found this symptom present seventeen times, and quotes Lamacq, who found it twenty-eight times in three hundred cases.

It is interesting to note the cause of the ataxia present in my case. The degeneration of the left posterior column, the posterior roots, as well as the interference with the transmission of sensory sensations by reason of the destruction of the nuclei of the posterior columns on the right side of the medulla, and degeneration of the right direct cerebellar tract, offer ample explanation for the presence of this symptom.

The hemiplegia, associated with ataxia, which was present in my case, was also described by Raymond-Cartaz.[50]

The points of special interest, on the part of the pathological findings in this case, are the presence of the pronounced meningitis, its probable syphilitic nature, the presence of ascending degeneration in the right pyramid of the medulla oblongata, and the bearing which the pathological findings have upon the cause, or causes, of cranial nerve involvement in syringomyelia and syringobulbia.

Disease of the meninges of the cord, medulla, and pons, which was present in my case, has been noted in a number of cases of syringomyelia and syringobulbia in the literature. The occurrence of pachymeningitis has been so frequent as to warrant the description of a "pachymeningitic type" of syringomyelia. It is characterized clinically by the presence of sharp pains in the distribution of the nerves of the cranium and spine, and other subjective sensory phenomena, symptoms which develop early in a number of cases of syringomyelia and syringobulbia.

Reference has been made to thirty-five cases in the literature of cavity formation in the cord or medulla oblongata, in which, at the autopsy, the meninges were found to be diseased.

Vulpian,[2] in 1861, described cavity formation in the anterior horns of the spinal cord, associated with chronic meningitis, and Simon,[3] in 1874, reported four cases in which the spinal cord was the seat of a cavity which was closely related, anatomically, to a co-existing specific leptomeningitis.

Zenoni[4] described a case in which leptomeningitis was present in a case of syringomyelia occurring in a child of three years. The cerebral meninges were opaque and thickened, and there was a fibrous leptomeningitis of the cord. Arteritis and periarteritis of the vessels of the spinal meninges and the cord itself were present. He stated that it was evident that the meningitis and the vascular lesions were of tuberculous origin.

In four cases reported by Rosenblath[5] there was pachymeningitis cervicalis hypertrophica associated with syringomyelia. He looked upon the pachymeningitis as having some etiological significance.

Achard and Joffroy[6] reported a case in which the cavity was closely related to the pachymeningitis. They believed that the syringomyelia in their case was the result of an inflammatory process having its origin in vascular disease and meningitic change.

In a case of syringomyelia reported by Jegorow there was meningitis of syphilitic origin in the sacral region.

In Hoffmann's[8] case, with bulbar symptoms, a chronic pachymeningitis cervicalis fibrosa was found, the cavity extending into the medulla.

Müller and Meder[9] described a case of cavity formation, associated with pachymeningitis, in which the pia and arachnoid were fused together in the cervical region.

Oppenheim[10] described a case of gliosis of the spine, extending from the cervical to the lower lumbar region, in which there were pachymeningitis and leptomeningitis.

In a case reported by A. Westphal[11] there was intense hemorrhagic pachymeningitis and leptomeningitis of the brain and spinal cord. The cavity extended from the third cervical to the third lumbar segment, and the medulla oblongata was the seat of numerous spaces or crevices in the pyramidal tract. He described two other cases of syringomyelia associated with pachymeningitis interna hemorrhagica, in one of which a general miliary tuberculosis was present. In the second case the spinal pia was thickened throughout its entire extent, as far as the medulla oblongata.

Saxer[12] quotes Charcot who was the first to describe pachymeningitis cervicalis hypertrophica. Charcot reported two cases, in one of which there was cavity formation.

In eleven cases with autopsy, reported by Phillip and Oberthur,[13] there was pachymeningitis. In some cases the arachnoid and pia were also involved. The pachymeningitis was slight in the region of the cord which was least affected by the syringomyelia, namely, the dorsal and lumbar regions. The pachymeningitis cervicalis hypertrophica was more intense at the levels of the cervical enlargement and the medulla oblongata, regions which presented the greatest amount of syringomyelia.

In a case reported by Kaiser and Kükenmeister,[14] the pia in the upper cervical region, and in the medulla oblongata, was very much thickened, and contained numerous dilated blood vessels with thickened walls.

Schwarz[15] cited a case of cavity formation in the anterior horns of the lower cervical region, and extending irregularly from the fourth dorsal segment to the thoracic region, associated with meningomyelitis syphilitica.

Jappha[16] described a case of cavity formation, which he looked upon as being due to syphilis. He designated his case as one of meningomyelitis syphilitica. Pachymeningitis spinalis gummosa and leptomeningitis were present.

Koehler[17] described a case of extensive leptomeningitis with cavity formation extending from the upper cervical to the middle dorsal region. There was central syringomyelia and widespread leptomeningitis.

H. S. Hutchinson[18] recently reported two cases of syringomyelia in which the meninges were involved. In one of his cases there was a history of syphilis, and the lesions in the vessels and meninges were explained on this basis.

In a case observed by Schultze[19] there was diffuse leptomeningitis spinalis, with transverse myelitis and cavity formation in the anterior part of the posterior column.

Wieting[20] described a case in which intense inflammatory thickening of the meninges and cavity formation in the cervical swelling were observed. He believed that the process had begun in the meninges. Intense pachymeningitis was also present in the case reported by Dercum and Spiller.

Whether the meningitis is the cause of the cavity formation in these cases, or whether both processes are the result of one cause, and whether that cause is syphilis or not, is still conjectural to a certain extent.

Phillip and Oberthur, as a result of their investigation of eleven autopsies, believed that the cavity formation and the pachymeningitis were the result of a common cause, and developed parallelly without being dependent one on the other. Adamkiewicz held to the same view. On the other hand Rosenblath considered that the pachymeningitis in his four cases were primary, and the syringomyelia the result of a disintegrating process (" einschmeltzungsprocesse ").

Schwarz admits that spinal meningitis is an etiological factor in the formation of cavities in the cord which does not differ in the strict sense from the cavity formation of syringomyelia.

In my case the character of the disease of the vessels of the cord and the medulla oblongata, the occurrence of round cell infiltration in the pia and around the blood vessels, and the presence of diseased blood vessels and round cell infiltration in the wall of the cavity at various levels, suggested the probability that these lesions were of syphilitic origin. Instances of this nature are not rare in the literature, and a number of cases have been reported in which cavity formation had occurred during the course of a specific meningomyelitis. Of such was the case of Schwarz, in which there was cavity formation in the anterior horns on one side, situated in the cervical, dorsal, and sacral regions. He cites a case, described by Lamy, of syphilitic myelitis with cavity formation which seemed to be related to the distribution of the vessels, and also Schultze's case, in which cavity formation was found associated with diffuse leptomeningitis spinalis and transverse myelitis.

Jegorow reported a case of syringomyelia associated with meningitis and syphilitic vascular change, and in Simon's four cases of syphilis there was cavity formation and spinal meningitis. The cases of Jappha, Nebelthur,[22] and Hutchinson must be mentioned in this connection. Jappha believed that the cavity formation in his case was the result of a syphilitic meningomyelitis, and Wieting concluded that syphilis is the cause in a great number of cases of pachymeningitis cervicalis hypertrophica with secondary involvement of the cord and cavity formation.

These observations warrant the conclusion that the presence of syphilitic disease of the cord and meninges in syringomyelia is probably more than a coincidence.

The presence of disease of the blood vessels in syringomyelia has been well recognized for a long time. There is usually an increase in the number of blood vessels, especially in the neighborhood of the proliferation of the pia, and in some cases numerous blood vessels are found clumped together in a small area, as was seen in the lumbar region of our case. In Westphal's case (quoted by Schlesinger) there were as many as ten vessels in one group. They are usually more numerous in the peripheral portion of the proliferated glia. The blood vessels are frequently distended and filled with blood.

Schlesinger quoted Simon and Meinert, who described an unusual delicacy ("zartheit") of the wall of the vessels, also cases in which the lumen of the vessels were contracted, and sometimes obliterated, as in the cases of Joffroy and Achard, Fürstner and Zachner,[23] Raymond,[24] Redlich,[25] Leyden,[26] Chiari,[27] and others. Schlesinger has never observed proliferation of the intima, although this has been described by Rosenblath, and was present in my case. In uncomplicated cases Schlesinger claims that round-cell infiltration of the walls of the vessels is not regularly present, but the lymph spaces are often distended.

The presence of thrombosis in the arteries, which was present in the basilar artery in my case, has been observed (though not frequently) by Joffroy, Achard, and others (quoted by Schlesinger).

In the opinion of Müller and Meder the degeneration of the vessels was responsible for the necrotic process present in their case, and Kölpen emphasized the fact that in his case the vascular conditions were closely associated with the gliosis. Many hemorrhagic necrotic foci were present. In Steudner's [28] case, with cavity formation, the vessels had undergone colloid degeneration. Joffroy and Achard believed that the vascular lesions are important factors in the formation of syringomyelic cavities.

Phillip and Oberthur found a great variety of vascular changes in their eleven cases of syringomyelia and pachymeningitis cervicalis hypertrophica, and in Jappha's case of syphilitic meningomyelitis, already referred to, the blood vessel alterations were striking. Syphilitic change in the vessels was present in Jegorow's case of syringomyelia associated with meningitis, and Joffroy and Achard looked upon the development of syringomyelia as the result of an inflammatory process, having its origin in disease of the vessels and the meninges.

In my case the findings have some bearing upon the explanation of bulbar symptoms in cases of syringomyelia and syringobulbia. It is well known that the lesion in syringobulbia does not extend beyond the lower part of the pons, except in the isolated case of Spiller,[29] in which the cavity was found as high as the posterior limb of the internal capsule just below the floor of the lateral ventricle. Involvement of the cranial nerves above the nucleus of the facial nerve is generally considered to be the result of some complication. In my case there was an involvement of the third nerve, causing ptosis; of the fourth nerve on one side, causing paralysis of the right superior oblique muscle; involvement of the fifth nerves, explaining the anesthesia of the left side of the face and on the right side of the scalp; and of the nucleus of the right twelfth nerve, causing right hemiatrophy of the tongue. There was also degeneration of the right ninth and tenth nerves, both eighth nerves, the right seventh, and both optic nerves. The degeneration, however, was of peripheral origin in all instances (except the right twelfth nerve) as the fibers of these nerves within the pons and medulla were apparently normal. In all probability the degeneration of the nerves described was due to pressure from the intense leptomeningitis to which they were subjected as they passed from the medulla oblongata and pons to their peripheral distribution. It seems probable, if this be true, that in some cases the symptoms in the distribution of nerves, above the seventh especially, may be due to degeneration of the nerves, the result of pressure upon them by a co-existing leptomeningitis. As far as I have been able to learn, this observation has not hitherto been made, although Kölpen[30] explained in this way the atrophy and paralysis in the upper extremity in his case of pachymeningitis cervicalis hypertrophica.

The presence of a cavity in the pyramids has not been frequently described. It was present on one side in my case, in a case of Spiller's, and in the right pyramid in a case observed by Raymond and Phillip (quoted by Wilson). It was found in both pyramids in Rosenblath's case, and in Wilson's[32] case the cavity, involving both olives, destroyed also partly the pyramids. In a case reported by A. Westphal, numerous spaces, or small cavities, were found in the region of the pyramidal tracts in the medulla oblongata, partly destroying the crossed pyramidal fibers.

Brief reference should be made to the distribution of the cavity in my case. It was limited to the left side of the cord, from the sacral to the second thoracic, at which level it involved also the right anterior horn, and this condition persisted to the fifth cervical segment, at which point, to the lower levels of the medulla oblongata, the cord was, unfortunately, lost at the autopsy.

The unilateral localization of the cavity is uncommon. It was present in the case reported by Kölpen, and in a case of Dercum and Spiller, who quoted Oppenheim as stating that only two cases of unilateral syringomyelia with autopsy are on record: those of Rossolimo, and of Dejerine and Sottas. They also refer to a case of Hatschek's which presented predominance of the lesion on one side.

The retrograde degeneration of the right pyramid in the medulla oblongata above the cavity in my case is deserving of some special mention. The presence of degeneration of the pyramidal tracts in the cord and medulla in an ascending direction is, however, not an uncommon observation. References in the literature to this condition, either in the cord or medulla, or both, not all, however, in cases of syringomyelia have been made by twenty-four observers.

Michaud, in 1871, believed that it was not rare to see sclerosis of the lateral tracts above the spinal lesion. With the exception of C. Westphal,[34] who described a case in which there was degeneration of one of the pyramids of the medulla oblongata above the lesion, most of the cases were reported in the last fourteen years.

In the cases of Goumbault and Phillip, Raymond, Sottas,[35] Murto,[36] Hutchinson, Dercum and Spiller,[37] Williamson,[38] and in one of Spiller's, the degeneration did not extend into the medulla oblongata.

In the cases reported by Hatschek,[39] Schultze, Miura,[40] Schlesinger, C. Westphal, Fürstner, Zachner, A. Westphal, Rossolimo,[41] Wieting, Petren,[42] Spiller[24] (in one of his cases), Wilson, and Lloyd,[43] the ascending degeneration was situated in the pyramids of the medulla oblongata.

The extent of the degeneration usually is limited to short distances, but, on the contrary, it may extend from the lower levels of the cord into the medulla oblongata and pons. In Petren's case the degeneration extended from the eighth cervical segment into the pons. In Hunt's[44] case the degeneration was found as high as the crura, and the degeneration extended from the lumbar region to the lower portion of the medulla oblongata in a case reported by Goumbault and Phillip. In Rossolimo's case of syringomyelia the degeneration extended from the dorsal region into the pyramids of the medulla, and in Fürstner and Zachner's case it extended from the lower lumbar region into the medulla.

Several theories have been advanced to explain the presence of ascending degeneration in the pyramidal columns, and in the pyramids of the medulla oblongata.

Schlesinger and Hatschek believed that the ascending degeneration of the pyramids was due to degeneration of the fibers connecting the cerebrum with the bulbar nerves. A. Westphal, however, could not reconcile the extensive degeneration in his case to this theory. He thought that the nerve fibers of the medulla oblongata during fetal life, before they were medullated, were subjected to some depressing influence which lowered their resistance to irritating influences later in life. Schlesinger later agreed that perhaps this, as well as his own theory, explained the degeneration.

A third explanation offered by Schlesinger was that, possibly, sensory fibers that were cut by the cavity normally had a cerebral course for some distance after decussating with the pyramidal fibers. This, he claimed, would explain contralateral degeneration in the pyramids. He acknowledged that this hypothesis had no anatomical foundation.

Fürstner and Zachner regarded degeneration of the pyramids in their case as an unusual form of degeneration, especially as it was associated with ascending degeneration of the lemniscus. Hunt considered the ascending "atrophy" in his case a retrograde process.

Obersteiner[45] viewed retrograde degeneration of the pyramidal fibers as a process very similar to the Wallerian degeneration, although in the former the axis cylinders remained intact longer than in the latter, an opinion shared by Klippel and Durante,[46] and Goumbault and Phillip, who stated that it differed from the Wallerian degeneration in the tardy development of the destruction of the myelin substance which occurred before that of the axis cylinders.

Sottas believed that it was in consequence of the destruction of certain cells in the gray substance which formed the axis cylinders, of which some ascend and some descend. He quotes Gudden, Farel and von Monakow, who have shown experimentally that the nerve fibers when separated from their centers degenerate in two directions, centrifugally and centripetally, but that the retrograde degeneration is only manifested in young animals, and appeared only after the lapse of a considerable time.

Von Bechterew and Ziehen (quoted by Petren) have demonstrated the presence of scattered fibers in the pyramidal tracts which do not belong to this system of fibers, and von Bechterew (quoted by Petren) believed that they consist of descending fibers originating in the cerebellum.

Von Bechterew[48] elsewhere described fibers which are situated in the posterior part of the ground bundle, between the pyramidal tracts and the gray substance, which he called the " mediales Seitenstrangbundel." It is made up of short fibers, and is related to the gray substance of the cord. In the guinea-pig these fibers degenerate upward, but this has never been demonstrated in man. It is possible that in some cases the ascending degeneration found in the lateral columns is due in part to degeneration of these fibers.

According to Egger (quoted by Spiller) retrograde degeneration attacks the short fibers in the pyramidal tracts, and the resulting sclerosis sets up a degeneration of the long fibers.

The ascending degeneration of the left lemniscus in my case, which was traced as high as the level of the nucleus of the fourth nerve, is really explained by the character of the lesion in the right side of the medulla. The cavity extended from a point a short distance to one side of the central canal, in a forward and outward direction, destroying the right olive, and cutting the internal arcuate fibers, besides the fibers of the twelfth nerve and the cerebellar olivary fibers.

Degeneration of the lemniscus has been described in a number of cases, in fact, according to Schlesinger, the degeneration of the contralateral lemniscus is a typical finding in the lateral cavity formation of the medulla oblongata. It has been observed by thirteen observers, viz.: Wieting, Müller, Meder, Kölpen, Hoffmann, Hatschek, Schlesinger, Wilson, Westphal, Rossolimo, Miura, and Phillip and Oberthür.

This degeneration is probably in some instances at least partially the result of destruction of the nuclei of the posterior columns, as in the cases of Hatschek, Schultze, Hoffmann, Miura, and Schlesinger, and my own.

Phillip and Oberthür (quoted by Wilson), who described degeneration of the lemniscus, stated that, in their opinion, it is a constant finding in advanced syringomyelia, basing their statement upon four examinations in which there was a gliosis beginning in the posterior horns.

LITERATURE.

1. Schlesinger. Die Syringomyelie, 1902.
2. Vulpian. In Schwarz.
3. Simon. Arch. f. Psychiatrie u. Nervenkrank., No. 5, 1874, 108.
4. Zenoni. Revue Neurologique, 1890, 924.
5. Rosenblath. Deut. Arch. f. klin. med., 1893, 210.
6. Achard and Joffroy. Neurologische Centralblatt, 1891.
7. Jegorow. Neurologische Centralbl., 1891.
8. Hoffmann. Deut. Zeit. f. Nervenheilk., 1892–93, 17.
9. Müller and Meder. Deut. Arch. f. klin. Med., 1895, 117.
10. Oppenheim. Neurologische Centralbl., 1892, 759.
11. A. Westphal. Deut. Arch. f. klin. Med., 1899, 355, and 1896.
12. Saxer. Centralbl. f. allgm. Path. u. Path. Anat., 1898, 59; and Ziegler's Beitrage, 1896, 332.
13. Philippe and Oberthür. Revue Neurologique, 1899, 907.
14. Kaiser and Kükenmeister. Arch. f. Psychiatrie, xxx, 250.
15. Schwarz. Zeitschr. f. klin. Med., No. 34, 1898 469.
16. Jappha. Deut. Med. Woch., 1899, No. 25, 299.
17. Koehler. In Schwarz.
18. Hutchinson. University of Pa. Med. Bull., March, 1906.
19. Schultze. Virchow's Archiv., 1882, 510.
20. Wieting. Ziegler's Beitrage, No. 19, 207; ibid., xiii, 411.
21. Adamkiewicz. Pachymeningitis Hypertrophica, Wien., 1890.
22. Nebelthur. Deut. Zeit. f. Nervenheilk., 1900, No. 10.
23. Fürstner and Zacher. Arch. f. Psychiatrie u. Nervenkrank., 1883, 422.
24. Raymond. Arch. f. Neurologie, 1894; and in Schlesinger.
25. Redlich. In Schlesinger.
26. Leyden. In Schlesinger.
27. Chiari. In Schlesinger.
28. Steudner. In Schwarz.

29. Spiller. Brit. Med. Journal, October, 1906, 1077.

30. Kölpen. Arch. f. Psychiatrie, 1895, 319, and 1906, 286.

31. Goumbault and Phillip. Arch. de Med. Experiment. de l'Anat. Path., 1894.

32. Wilson. Revue de Med., 1904, 685.

33. Michaud. Theses Sur La Meningitis Et. La Myelitis Dans Le Mal Vertebrale, 1871.

34. C. Westphal. Arch. f. Psych. u. Nervenkrank., 1874, v, 90.

35. Sottas. Compte rend. de la Soc. Biol., 1893, 925.

36. Murto. In Durante.

37. Dercum and Spiller. American Jour. of Med. Sciences, 1896, 672.

38. Williamson. Brit. Med. Jour., 1893, 946.

39. Hatschek. Wiener Med. Woch., 1895, 1027.

40. Miura. In Hatschek.

41. Rossolimo. Arch. f. Psych. and Nervenheilk., 1899, 1890, 897.

42. Petren. Nordish Medicinsk. Arch , 1901, No. 14, 1.

43. Lloyd, J. H. University of Pa. Med. Mag., 1892, v, 293.

44. Hunt. Jour. of Nervous and Mental Dis., 1904, 504.

45. Obersteiner. Nervösen Central Organe.

46. Klippel and Durante. Revue de Med., 1895, No. 15.

47. Durante. Revue Neurologique, 1894, 390.

48. Von Bechterew. Neurologische Centralb., 1897, 6, and Die Leitungs Bahnen in Gehirn und Ruckenmark.

49. Spiller. Johns Hopkins Bull., 1898, 125

50. Raymond-Cartaz. Gazette des Hopiteaux, 1895, Nos. 21 and 34.

DESCRIPTION OF PLATES II. AND III.

FIG. 1. — Showing intense leptomeningitis and distorted medulla oblongata.

FIG. 2. — Cavity in posterior portion of the medulla oblongata. Degeneration of the right pyramid above the cavity in the pyramid, and of the left lemniscus and cerebellar-olivary fibers.

FIG. 3. — Cavity in right pyramid, and a second cavity destroying the nuclei of the posterior columns on the same side, the fibers of the twelfth nerve and the internal arcuate fibers. The left median lemniscus is degenerated and also the left cerebellar-olivary fibers.

FIG. 4. — Degenerated optic nerve.

FIG. 5. — Shows degeneration of the lemniscus on one side.

FIG. 6. — Cervical region. Cavity on the right side. Intense leptomeningitis. Grained fibers degenerated on the right side.

FIG. 7. — Thoracic region. Cavity in the left anterior and posterior horns. Degeneration of both crossed pyramidal tracts and right direct pyramidal tract.

FIG. 8. — Lumbar region. Cavity involving the anterior and posterior horns on the left side.

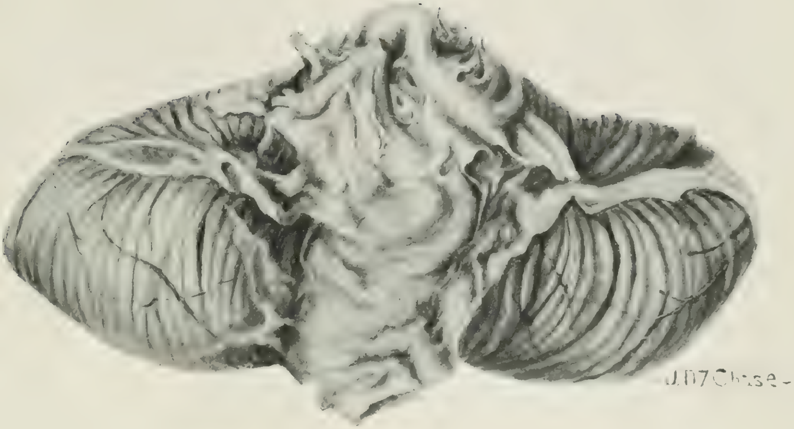


FIG. 1.

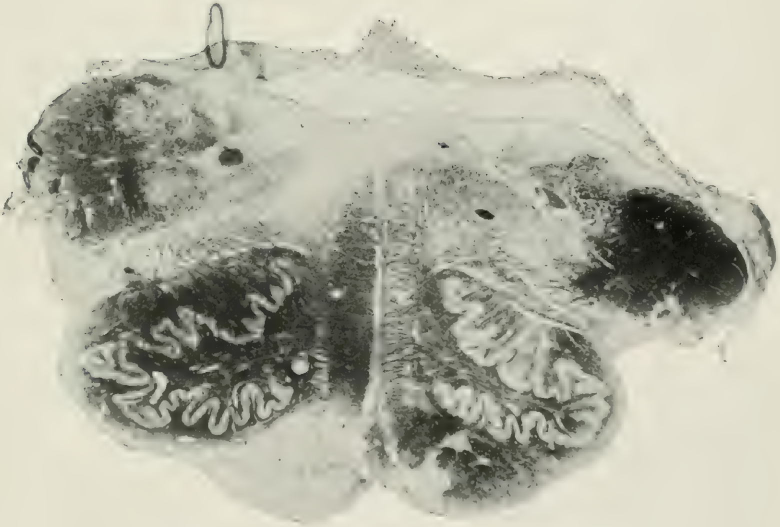
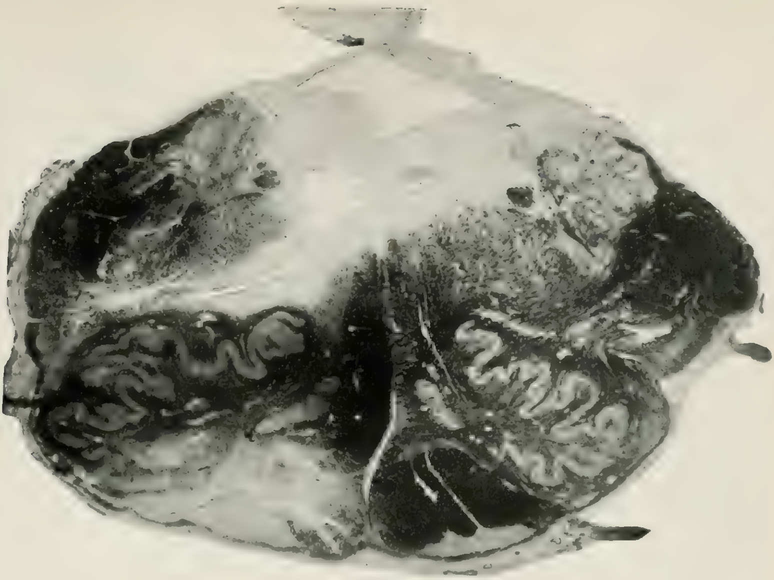


FIG. 2.



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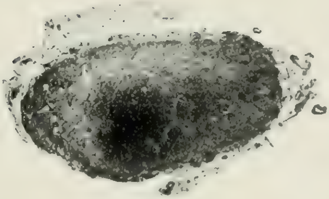

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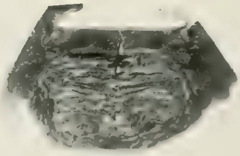

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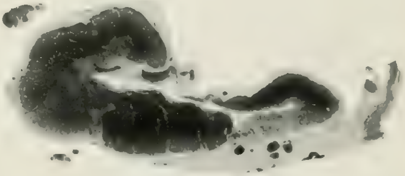

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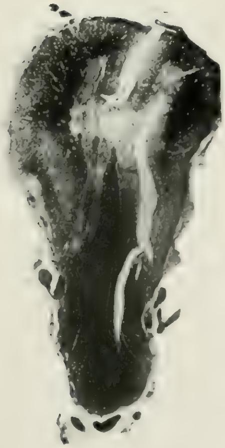

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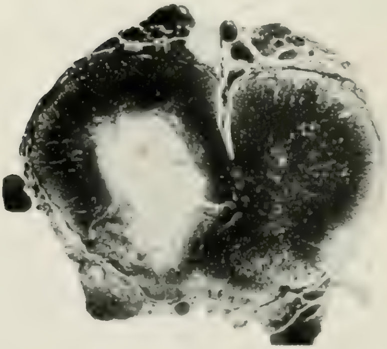

FIG. 8.

Rhein.

Syringomyelia with Syringobulbia.

THE ASSOCIATION OF SYRINGOMYELIA WITH TABES DORSALIS.*

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A few cases of tabes with syringomyelia are reported, and it is remarkable that with one exception (Philippe and Oberthur) they are all by German authors. The case that I have studied is therefore the first to appear in either American or English literature. Several writers have held that the association of the two processes is not merely a coincidence, but that one stands to the other in the relation of cause and effect; others have expressed themselves guardedly. It should be remembered that if one of these processes is in causal relation to the other, the simultaneous occurrence of the two disorders should be far more frequent than the few reported cases indicate. In several of these cases the degeneration of the posterior columns has been of the variety known as syphilitic tabes, with thickening of the blood vessels of the cord and round cell infiltration of the pia. Much has been written about this form of tabes[1] and it is the form occurring in my case. Martin Kirschner has written a thesis on the occurrence of syringomyelia with tabes dorsalis. He divides the published cases into three classes: (1) Those in which the symptoms of tabes predominate. (2) Those in which the symptoms of each disorder are pronounced. (3) Those in which neither group of symptoms is so distinct that a diagnosis of either of the two processes would be possible.

Under the first heading he puts the cases of Friedreich, Oppenheim (two cases), Jegerow, Eisenlohr, Nonne, Saxer, and Kirschner. Under the second heading the cases of

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* Read at the meeting of the American Association of Pathologists and Bacteriologists, May 7, 8, and 9, 1907. Received for publication Jan. 14, 1908.

Fürstner and Zacher, and Schlesinger. Under the third heading the cases of Simon, Schüle and Nebelthau.

Kirschner[2] does not venture to form a definite opinion regarding the relation of the tabes to syringomyelia in his case. Simon's[3] case (Case IV.) was one of dilatation of the central canal in the lower cervical and upper thoracic regions with tabes, and without symptoms of these spinal changes. Probably, therefore, it was not one of true syringomyelia. Moderate dilatation of the central canal is not a very rare finding. Jegerow's[4] case is very briefly reported. The patient was syphilitic and had paraplegia inferior with atrophy, loss of tendon reflexes, anesthesia, and loss of pupillary reflex to light. He had tabetic degeneration of the cord, meningitis of the sacral portion of the cord, and syphilitic changes of the vessels. The case is so briefly reported that it is impossible to form a positive opinion regarding it. Redlich, in his report of a case of hydromyelia with tabes, without clinical history, expressed the opinion that the contraction of the posterior columns caused disturbances of circulation and thereby nutritive changes in the peri-ependymal substance of the central canal. Eisenlohr's[6] patient had typical tabetic degeneration of the posterior columns, chronic posterior spinal leptomeningitis, and syringomyelia, and was in the tertiary stage of syphilis. The syringomyelia was in the cervical and upper thoracic regions. Eisenlohr believed that the gliosis of the left posterior columns originated from the tabetic proliferation of the posterior columns, and excluded a mere chance occurrence of the two processes, even though the syringomyelia was in the portion of the cord most commonly affected by this lesion, viz., cervical and upper thoracic regions. The case presented only symptoms of tabes, except possibly vasomotor disturbances. Nonne[7] thought there was some causal relation between the two processes in his case of tabes with syringomyelia, but expresses himself rather guardedly. The condition of the basilar artery suggested syphilis, although the spinal membranes were intact.

Oppenheim,[8] in reporting his second case in 1893, thought it probable that the tabes and syringomyelia had some relation to one another, especially as five or six well observed cases of the association of the two diseases were on record. Gliosis has a tendency to implicate the posterior columns and he believed it probable that in this way the tabes was produced in his two cases, *i.e.*, the tabes was secondary to the syringomyelia. No important changes were found in the spinal membranes in Oppenheim's second case, although he speaks of a considerable endarteritis of the anterior spinal artery, and this might suggest syphilis.

In a case observed by Saxer[9] (Case V., p. 376) the lesions of typical tabes were combined with a cavity extending almost the entire length of the cord. He did not regard the syringomyelia as a chance complication of the tabes. The destruction of tissue (syringomyelia) he believed was caused by disturbance in the nutrition, and this disturbance was produced by tabes.

In Case XX., reported by Philippe and Oberthur,[10] the lesions of tabes were associated with a dilated central canal. It was not, therefore, true syringomyelia, and no particular attention was called to the association of the two processes. Nebelthau,[11] in discussing his case of syringomyelia with degeneration of the posterior columns of the cord, expresses the opinion that syphilis was probably the original or at least predisposing cause of the two processes. His case was one of syphilitic tabes. In support of this opinion he refers to the fact that syphilis was the cause of the disease of the posterior columns of the spinal cord in the cases of Eisenlohr, Jegerow, Nonne, and Westphal. Ernest Frey's[12] case is very briefly reported. The tabes was associated with syringomyelia in the cervical region. Syphilitic leptomeningitis was present. Frey believed an etiological relation existed between the tabes and the syringomyelia, but he could not determine whether a syphiloma developed around the central canal and later disintegrated, or whether the syphilis only gave an impulse to the development of the syringomyelia. The meaning of the last statement is not very clear.

Schlesinger[13] presents the subject very clearly. He reports a case in which the clinical symptoms of tabes preceded those of syringomyelia. The cavity in the cord in general appeared like a dilated central canal, inasmuch as it had an epithelial lining. The degeneration of the posterior columns was typically that of tabes. The central proliferation of neuroglia in places passed diffusely into the sclerosis of the posterior columns, but in the greater portion of the cord was sharply defined. He was unable to find any causal relation between the tabes and syringomyelia, although he believes that each process was modified by the other. It is possible, he thinks, that a circumscribed, tumor-like gliosis may arise from the secondary degeneration of tabes; this, however, seems to me very doubtful; but it is more probable, Schlesinger thinks, that such does not occur, as in no other form of secondary degeneration do we find tumor-like proliferation of the neuroglia. It is probable that certain unknown differences exist between the proliferation of neuroglia in secondary degeneration and that in tumor-like form, greater than a mere quantitative one; so that one type does not pass readily into the other. The neurogliar proliferation in tabes is reparative; in syringomyelia it is destructive. Schlesinger quotes the opinion of Philippe and Oberthur, viz.: that the ependyma proliferates very readily in chronic disease of the spinal cord because of the irritation produced, and believes that the hydromyelia associated with tabes is secondary. He thinks the proliferation of the ependyma occurs too seldom to be regarded as a secondary process. He acknowledges, however, that the pulling caused by the contracting posterior columns, when changes already exist in the gray matter, may exert such an irritation as mentioned above upon the wall of the central canal, and may produce circulatory disturbances; but this does not mean that one process arises from the other, but that one is modified by the other. It may be questioned, I think, whether the contraction of the neurogliar tissue in the posterior columns causes any appreciable pulling upon the central gray matter. It should be remembered also that the vascular supply of the two areas is not the same.

The origin of tabes in syringomyelia is extremely improbable Schlesinger thinks. Syringomyelia develops mechanically and cannot produce the systemic degeneration of tabes. The two processes are coördinated, but both may be secondary to syphilitic disease of the meninges, which causes degeneration of many posterior roots and also softening and cavity formation in the spinal cord.

He refers also to cases of tabes and syringomyelia observed by Pick, Vučetic and Roth (these I have not been able to find) and says he has seen the simultaneous occurrence of the two processes in two cases and also the preparations of two other cases, one of which was Redlich's.

The opinions that Schlesinger has expressed correspond very closely to my own. In the case I have studied the degeneration of the posterior columns from the mid-lumbar region downward was typical of tabes in the preservation of the ventral fields and the small zone along each side of the posterior septum (septo-marginal tract). At these levels of the cord no cavity was found. It would be impossible to attribute this degeneration at these levels to syringomyelia. Where the cavity first appeared in the upper lumbar region it was evidently merely a dilatation of the central canal and could hardly have been caused by the tabes. Still higher where the cavity was extensive and was more than hydromyelia, the glia in many levels formed a dense band of tissue about it, much denser than, and at certain levels distinct from, the neurogliar proliferation of the posterior columns. In some regions the vessels throughout the greater part of a transverse section were sclerotic. This may have been caused by the syphilis, but it seems to me probable that it was in greater part the vascular thickening not uncommon in syringomyelia, especially when near the thickened glia about the cavity. I therefore find it impossible to believe that either process is in causal relation to the other. Were this causal relation existing we should find the two disorders occurring together much more frequently, as tabes is a very common disease, and true tabetic degeneration associated with syringomyelia is certainly a very rare finding.

The clinical history of my case justified the diagnosis of tabes associated with syringomyelia made by me seven or eight years before the patient's death. The diagnosis of syringomyelia had previously been made because of the dissociation of sensation, scoliosis and deformity of one hand. Some seven or eight years ago, after studying the history and examining the patient carefully, I made the diagnosis of tabes in addition to syringomyelia, on account of the commencement of the symptom-complex with ataxia and shooting pains in the lower limbs, loss of tendon reflexes in these limbs, optic nerve atrophy, myopia and Argyll-Robertson pupils. Syringomyelia involving the posterior columns may cause some of the symptoms of tabes and the loss of the tendon reflexes of the lower limbs might be explained in this way. The lumbar region of the cord is not likely to be implicated first by syringomyelia, and even if the process had commenced here the cavity would probably be in the center of the cord and the reflex arc of the patella tendon on each side might be pushed to one side and escape, as I[14] have seen occur in intense syringomyelia of the lumbar region. The commencement with pain, ataxia, and loss of tendon reflexes in the lower limbs is very common in tabes, rare in syringomyelia, and when optic nerve atrophy and Argyll-Robertson pupils were found the diagnosis of true tabes or syphilitic tabes seemed probable. Scoliosis may occur in tabes, and I[15] have reported such a case, but in association with the intense sensory disturbances largely of the syringomyelic character and the atrophy and deformity of the left hand, the diagnosis of syringomyelia had to be retained. The case therefore seemed to be one of tabes associated with syringomyelia. The degeneration of the median fillet of one side resulting from a cavity in the medulla oblongata and followed as high as the cerebral peduncle is an interesting finding in the case. The history of my case is as follows:

J. S., about sixty years of age, white, male, was admitted to the Philadelphia General Hospital May 22, 1886, and died there Aug. 9, 1906. He had often been studied by members of the Neurological staff and was frequently used by me in my lectures.

The symptoms began in 1875 with staggering while walking in the dark, and he fell at times. Sharp shooting pains in the lower limbs began in 1889, and he often complained of these pains to me nearly to the time of his death. In 1891 he had ataxia of his hands and could not hold his pen properly in writing. Incontinence of urine commenced in 1900. He complained of a sensation as if he were walking on rubber, and of girdle-like pains across the chest. The scoliosis was first noticed in 1893, and since that time he had been unable to walk on account of weakness and ataxia of the lower limbs. He complained of tingling and numbness in the fingers and forearms, the little finger of the left hand became contracted, and later all the fingers of the left hand were similarly affected. Atrophy of the thenar and hypothenar eminences and of the interossei muscles of the left hand developed. The bowels were usually constipated. He denied syphilitic infection.

He was intelligent. His speech was not affected. The cranial nerves, except the optic, were in good condition. The scapular and deltoid muscles, especially the muscles of the left shoulder, were much atrophied. The upper limbs were ataxic and wasted, especially the left, and the alteration was more intense in the distal part of this limb. The voluntary power of the upper limbs was impaired, especially of the left limb, but the upper limbs were not paralyzed except in the left hand. The tendon reflexes of the upper limbs were lost.

The lower limbs were almost completely paralyzed.

The patellar reflexes were lost and ankle clonus was not obtained. Babinski's sign was present on each side. The sensation was tested many times, but the charts show variations in extent and intensity. All forms of sensation were much affected in the lower and upper limbs and trunk. For a period tactile sensation was less disturbed. The man complained much of painful contracture of his lower limbs. These limbs were not much atrophied. Pes valgus was present on each side.

An examination of the eyegrounds made by Dr. de Schweinitz, the date of which is not given, showed myopic pupils and gray atrophy of the nerves. A report from Dr. Oliver, dated Jan. 8, 1902, stated that the irides were almost immobile to light stimulus thrown from all peripheral portions of the visual fields, and the best response was obtained when the light was thrown from the nasal side of the left field. The optic nerve heads were quite gray in their deeper layers, and the retinal arteries were diminished in size. The iridic response was prompt in accommodation and convergence. The extraocular muscles were not affected.

Dr. Oliver reported Feb. 23, 1905: Vision of the right eye uncorrected, 5/15; of the left eye, 5/10. Pupil of the right eye two millimeters in diameter; of the left eye, 1.5 millimeters. Iris very sluggish to light stimulus, especially that of the left eye. The extraocular muscles are unaffected.

Death occurred Aug. 9, 1906, while the patient was in the service of the late Dr. Wm. C. Pickett. Dr. Pickett spoke of giving the material to me as the diagnosis of tabes with syringomyelia had been made by me, and after the sad termination of Dr. Pickett's promising career, the brain and cord of the patient were generously placed in my hands for examination by Dr. Buckley.

The microscopical examination gave the following results:

Upper and middle sacral and lower lumbar regions. — The posterior columns are much degenerated and in sections from the higher levels the crossed pyramidal tracts are also degenerated. The ventral fields and a zone along the posterior septum are intact. The degeneration is typical of tabes. Round cell infiltration is present in the pia. The region of the central canal shows nothing abnormal.

Mid-lumbar region. — The degeneration of the posterior columns is characteristic of a marked case of tabes. The cavity in the central gray matter begins at this level, and seems to be merely a dilatation of the central canal, as the opening is surrounded at nearly all parts by a layer of ependymal cells. The cavity formation at this level has no connection with the posterior columns, and the ventral fields of these columns still contain many normal nerve fibers. The cavity becomes extensive at the second lumbar segment, and extends as a narrow slit through the left posterior horn, and in this portion has no lining of ependymal cells, but the portion in the central gray matter is well lined with these cells. The small blood vessels in the central gray matter have much thickened walls. As the vessels elsewhere in the section are not much thickened, the sclerosis of those within the central gray matter is probably caused by the syringomyelia. No distinct connection can be seen between the central sclerosis and that of the posterior columns.

At the twelfth thoracic segment the cavity is confined to the central gray matter and is surrounded by an area of dense neurogliar tissue, much denser than the sclerosis of the posterior columns and quite sharply differentiated from it. Much of the cavity is lined by ependymal cells. The small blood vessels in all the white matter show thickened walls.

At the tenth thoracic segment the cavity is a narrow slit extending laterally through the gray matter. The posterior columns are intensely degenerated; the crossed pyramidal tracts are only a little less degenerated as a result of the syringomyelia.

The cavity becomes much smaller at the ninth thoracic segment, and is surrounded by a denser layer of neurogliar tissue than in the tenth thoracic segment; and it is much denser than the neurogliar proliferation of the posterior columns. This dense central area is rarefied at the center of one of the anterior horns near the central canal.

The sixth thoracic segment shows the cavity again as a narrow slit extending through the central gray matter and into one posterior horn.

At the fourth thoracic segment the neurogliar proliferation about the cavity is more pronounced and forms a part of the sclerosis of the posterior columns.

The cord is very much flattened at the eighth cervical segment and the cavity extends through the central gray matter and into each anterior horn, destroying almost entirely the left anterior horn but leaving a large portion of the other anterior horn intact. This gives the explanation for the intense atrophy of the left hand. The posterior columns are intensely degenerated. The round cell infiltration is pronounced throughout the spinal pia.

A portion of both anterior horns is preserved at the seventh cervical segment, and the complete destruction of the left anterior horn seen at the eighth cervical segment is not present here, therefore the left forearm was not intensely atrophied. The small blood vessels of the pia are thickened.

The fifth and sixth segments resemble the seventh segment closely. The cord begins to assume more of its normal shape at the fourth cervical segment, although the cavity is still extensive.

The cavity disappears at the third cervical segment.

Sections from the medulla oblongata show a narrow slit in the position of the intramedullary roots of the ninth and tenth nerves, which has cut and destroyed the internal arcuate fibers of one side, so that the fillet of the opposite side is degenerated. This is rather a rare finding in syringomyelia. The degeneration of this median fillet is followed as high as the cerebral peduncle. The posterior longitudinal bundle on the side of the degenerated fillet is not so wide as that of the opposite side, and from this finding one might conclude that this bundle is formed partly by the internal arcuate fibers.

The optic chiasm is not degenerated. A transverse section of the left optic nerve shows many atrophied bundles of nerve fibers peripherally situated.

[I am indebted to Dr. Alfred Reginald Allen for the photographs.]

REFERENCES.

1. vide Nonne. Archiv. für Psychiatrie, xxiv, 1892, 526.
2. Martin Kirschner. Syringomyelie und Tabes dorsalis. Inaugural Dissertation. Strassburg. 1904.
3. Simon. Archiv. für Psychiatrie, v, 1875, 128.
4. Jegerow. Neurologisches Centralblatt, 1891, 406.
5. Redlich. Zeitschrift für Heilkunde, xii, 1891, 571.
6. Eisenlohr. Society Report, Archiv. für Psychiatrie, xxiii, 1892, 603.
7. Nonne. Archiv. für Psychiatrie, xxiv, 1892, 526.
8. Oppenheim. Archiv. für Psychiatrie, xxv, 1893, 315.
9. Saxer. Ziegler's Beiträge, xx, 1896, 376.
10. Philippe and Oberthur. Archives de Médecine Expérimentale, xii, 1900, 651.
11. Nebelthau. Deutsche Zeitschrift für Nervenheilkunde, xvi, 1900, 169.
12. Ernest Frey. Centralblatt für Nervenheilkunde und Psychiatrie, 1902, 240.
13. Herman Schlesinger. Die Syringomyelie. Franz Deuticke, 1902, 2d Edition, 331.
14. Dercum and Spiller. American Journal of the Medical Sciences.
15 Spiller. Philadelphia Medical Journal.

DESCRIPTION OF PLATES IV. AND V.

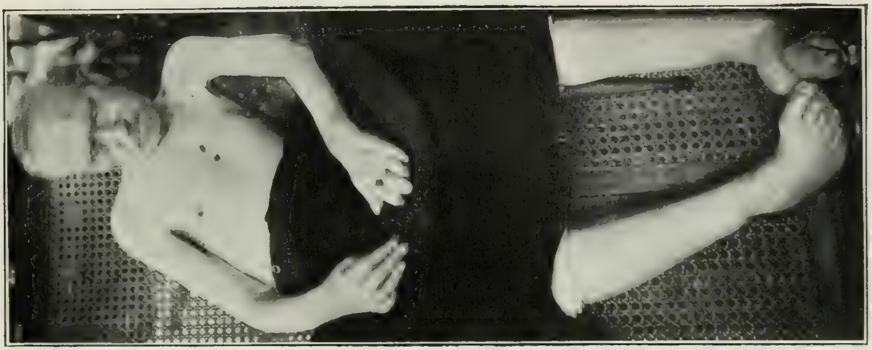
FIG. A. — Syringomyelia and tabes. The intense atrophy of the left hand was caused by complete destruction of the left anterior horn at the eighth cervical segment.

FIG. B. — Fourth or fifth lumbar segment. The degeneration of the posterior columns is tabetic in type.

FIG. C. — Second lumbar segment. The syringomyelia begins to be more extensive than it was in the segment below.

FIG. D. — Section from the seventh cervical segment. The cavity extends from one side of the cord to the other.

FIG. E. — Degeneration of the fillet of one side from destruction of the internal arciform fibers of the opposite side, resulting from a slit-like cavity in the opposite side in the course of the ninth and tenth nerves.



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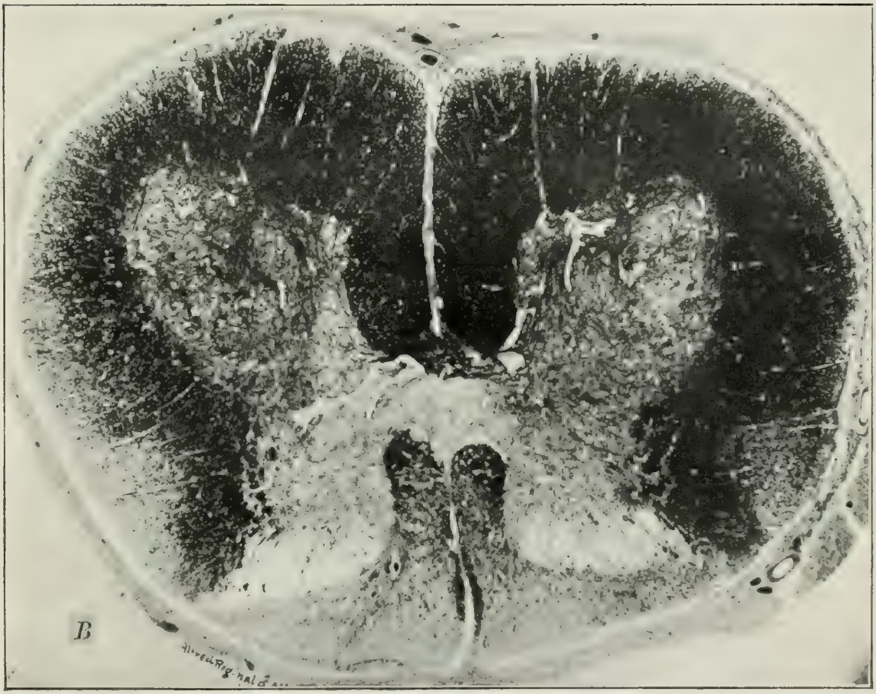
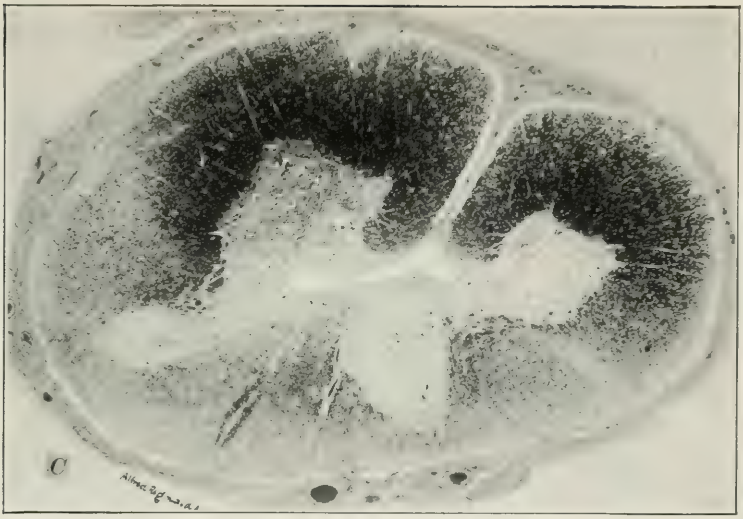


Spiller. Syringomyelia with tabes dorsalis.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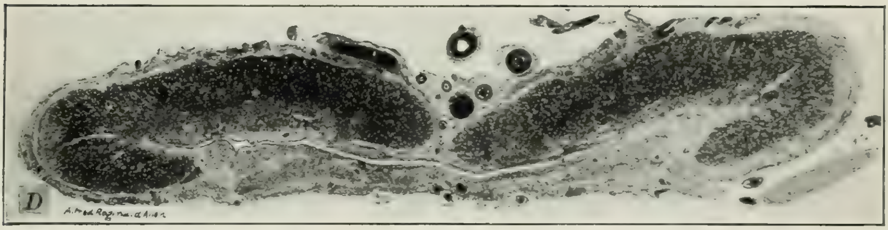
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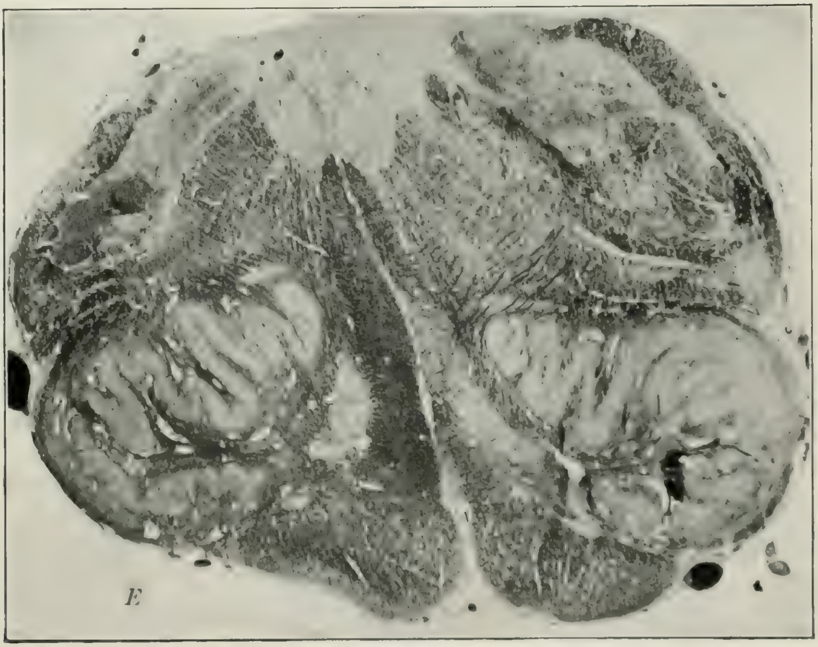
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Spiller. Syringomyelia with tabes dorsalis.

A FURTHER CONTRIBUTION TO THE STUDY OF BENIGN CYSTIC EPITHELIOMA.*

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As one of its many titles indicates, benign cystic epithelioma is commonly regarded as a non-malignant affection; but as our knowledge of its clinical course and histopathology grows it becomes more and more questionable whether the designation benign is properly bestowed upon this neoplasm. The number of cases in which ulceration occurs, resembling that which takes place in ordinary epithelioma, is too large to be the result of mere coincidence, and it seems as if we ought to revise somewhat our notions concerning the innocent character of this growth. So early as 1890 Hallopeau, under the title Eruptive Hydradenoma Complicated by Epithelioma, reported a case belonging to this group, in which epithelioma-like ulceration occurred, a case to which we shall refer again. A few years later Dr. James C. White, at a meeting of the American Dermatological Association, reported a second in which a number of the lesions showed destructive ulceration. presenting appearances indistinguishable from those of ordinary ulcerating epithelioma; and this author then expressed the opinion that it would probably be found that, if the cases were under observation for a sufficiently long period, such ulceration would occur in all of them.

Subsequently Jarisch, Stelwagon, and I each reported cases in which similar ulcerative changes occurred. Moreover, in one of the cases reported in my first paper it was found that, after removal of a confluent patch of small tumors upon the back, there was a recurrence at the margin of the cicatrix; and I have since learned from Dr. Charles N. Davis, to whom I was indebted for the opportunity to study

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* Received for publication Jan. 14, 1905.

the case, that more recent attempts at radical cure by the curette have likewise been followed by a return of the growth. To these cases I now desire to add another in which so many of the tumors underwent ulceration that it seemed likely that all of them would eventually exhibit this destructive tendency.

Miss H., twenty-nine years old, came under observation in June of last year, seeking treatment for an affection of the skin which consisted of numerous shot- to pea-sized, flat, sessile tumors scattered about over the forehead, eyelids, cheeks, nose, and sides of the neck. These little tumors were pinkish or red, for the most part discrete, but in a few places, as upon the cheeks and sides of the neck, aggregated in flat patches the size of a finger nail. Several of them were covered with brownish crusts beneath which were shallow ulcers, and upon the end of the nose was an oval, rather deep ulcer about a quarter of an inch in its largest diameter with an elevated, rounded border indistinguishable from the ordinary epitheliomatous ulcer. The first tumors had made their appearance a number of years ago, and new ones had continued to appear from time to time ever since. After an indefinite duration some of the lesions began to ulcerate, the largest and deepest ulcer being the one upon the end of the nose already referred to. Apart from slight itching and tingling the disease was unattended by any definite subjective symptoms.

Over the left malar eminence was a patch of shot-sized, partly confluent tumors as large as a thumb-nail, the center of which was just beginning to ulcerate; and from the margin of this patch several lesions were excised for purposes of microscopic study. The sections presented the appearances characteristic of benign cystic epithelioma. Beneath the epidermis, which presented nothing abnormal worth noting, there were numerous round, oval, and irregularly-shaped masses of cylindrical epithelium about the margins of which the cells were arranged radially, producing the palisade-like appearance noted by Brooke and others, while the center of the larger masses was occupied by cavities without definite walls, containing granular débris, occasionally small masses of dark brown pigment, and, in a few instances, what appeared to be fragments of disintegrated hair-shaft. In a number of sections these cell masses seemed to start from the overlying epidermis, but if they were followed through a sufficiently large series they were invariably found to have their origin in a hair follicle, and in no instance could they be traced to any other structure.

In connection with this case I have gone over again the material obtained from the cases observed during the past five years, including a second, unpublished one of Dr. C. N. Davis, which he was kind enough to permit me to make sections of, and this new study has fully convinced me of the entire correctness of Jarisch's statement that this neoplasm originates in the hair follicles alone. In my first paper, published some years ago, I stated that the neoplastic cell masses started sometimes from the basal cell layer of the epidermis, sometimes from the hair follicle, but I am now convinced of the inaccuracy of this statement so far as it concerns the epidermis; the hair follicle alone is the point of departure for the growth. The examination of a large number of sections obtained from four or five cases seems to show conclusively that the masses of cylindrical cells are nothing more than enormously overgrown and more or less distorted hair follicles the central cavities of which have been transformed into pseudo-cysts by the degeneration of their inner walls. The masses of pigment frequently observed in the smaller cavities probably arise from disintegration of pigmented hair shafts. In view of all the foregoing facts the name proposed by Jarisch — trichoepithelioma — is certainly the most appropriate of the many given to this neoplasm and ought, therefore, to be employed to the exclusion of all others.

A final word as to the relationship between benign cystic epithelioma and the much-named neoplasm variously known as syringoma, syringocystoma, syringocystadenoma, hemangioendothelioma, nevus cystepitheliomatosus, etc., these various names indicating the differences of opinion existing among authors as to the nature of the growth. Although still regarded as an endothelial tumor by some authors, most consider it epithelial, having its origin in the ducts of the sweat-glands, although such origin has not yet, so far as I have been able to learn, been actually demonstrated.

In a paper read before the British Medical Association at Oxford, in 1904, I reported a case of tumor of the skin, occurring upon the chin of a young girl, which corresponded accurately in every histological detail with the cases reported by Jarisch, Neumann, and others as syringoma or hemangio-endothelioma. In this case I succeeded, as I believed (and still believe), in demonstrating the origin of the neoplasm in the hair follicle, being utterly unable, unlike the authors mentioned, to trace any connection of the growth with either the sweat-gland apparatus or the endothelium of the blood vessels.

I also concluded that, while there were some marked differences in the histopathology of the two affections, there was a close relationship between this neoplasm and the so-called benign cystic epithelioma of the Brooke-Fordyce type, the former being in fact only a variety of the latter. In connection with this new study of benign cystic epithelioma I have also made new and extensive series of sections of this tumor of the chin for the purpose of correcting or verifying my previous conclusions, and to determine still more definitely, if possible, its place of origin, its nature, and relationship to the tumors resembling it.

To very briefly recapitulate the features of this growth, it is composed of numerous slender, curved, and branching tracts of cylindrical epithelium resembling superficially the ducts of the sweat-glands, but always without any sign of a central lumen, and variously-sized round and oval cysts filled with hyaline material, connected frequently with these duct-like tracts. In many sections slender epithelial tracts can be seen branching off from the sides of the hair follicles, usually from the upper half, while the cysts are in many cases simply dilated follicles, or are situated in the sebaceous glands. The more carefully this case is studied the more it seems to prove incontestably the follicular origin and epithelial character of the so-called syringocystoma; and in proving this also to demonstrate its relationship to benign cystic epithelioma. Furthermore, it seems to me not to be without significance as to the relationship of these two neoplasms that epithelioma-like ulceration may occur in the former just as in the latter, as is demonstrated by the case reported by Hallopeau previously referred to.

The results of this recent careful study of material collected during some years may be epitomized in the following conclusions:

1. So-called benign cystic epithelioma is an epithelial neoplasm having its origin in the hair follicles, and in these structures alone. In view of its follicular origin the name given it by Jarisch — trichoepithelioma — is most appropriate, and should be used to the exclusion of the many others used.

2. Since, in a fair proportion of cases, destructive ulceration has been observed, as well as a tendency to recurrence after removal, the affection can no longer be regarded as a benign one.

3. The tumors variously described as syringoma, syringocystoma, hemangioendothelioma, etc., have no relationship with the sweat-gland apparatus, nor the blood vessels, but are epithelial neoplasms having, like benign cystic epithelioma, their origin in the hair follicles.

4. The so-called syringocystoma is closely related to benign cystic epithelioma; both are composed of cylindrical-celled epithelium; both have their origin in the hair-follicles; both may undergo destructive ulceration; in a word, both are varieties of trichoepithelioma. The former probably originates in the slender lateral spurs frequently normally present in the lanugo; in benign cystic epithelioma the follicles as a whole are involved in the abnormal growth, these differences in the mode of origin and growth being amply sufficient to explain the differences in their histopathology.

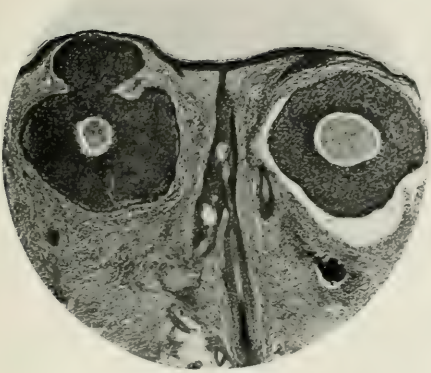

FIG. 1.

Benign Cystic Epithelioma.

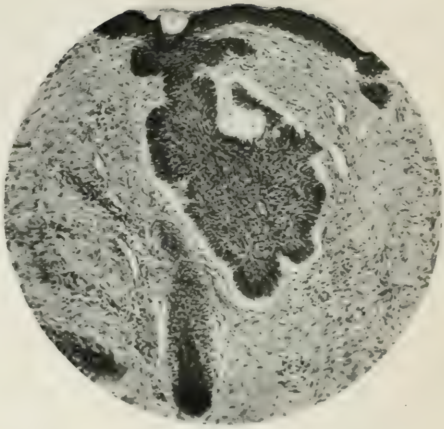

FIG. 2.

Benign Cystic Epithelioma. Showing origin of neoplastic epithelial mass from hair-follicle.

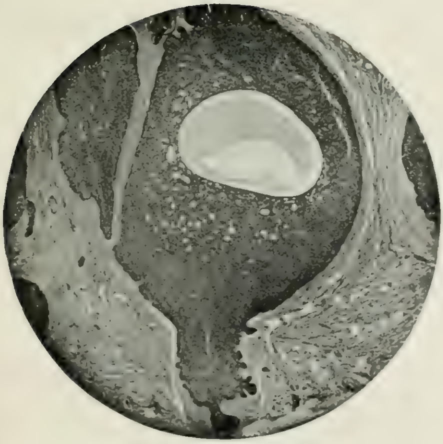

FIG. 3.

Benign Cystic Epithelioma. Greatly enlarged hair-follicle containing one large and numerous small cysts.

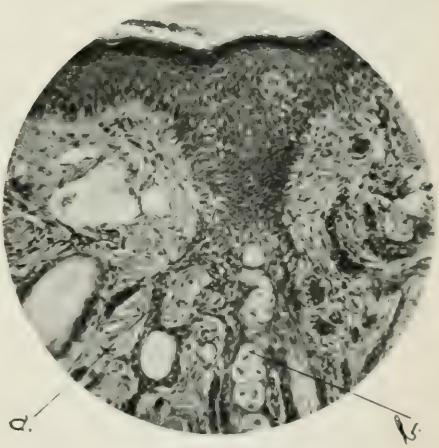

FIG 4

So-called Syringocystoma. Branching duct-like tracts of cylindrical-celled epithelium, (a) originating in hair follicle; (b) sebaceous gland.

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